Original Article

Differences in the Presentation and Outcome between Premenopausal and Postmenopausal Primary Hyperparathyroidism Indian Women: A Single-Center Experience

Aasim N. Maldar, Nishitkumar F. Shah, Phulrenu H. Chauhan, Murad Lala[1], Milind V. Kirtane[2], Manoj Chadha

Departments of Endocrinology, [1]Surgical Oncology and [2]ENT Surgery, P. D. Hinduja Hospital and Medical Research Centre, Mumbai, Maharashtra, India

ABSTRACT

Introduction: Primary hyperparathyroidism (PHPT) is an endocrine disorder wherein enlargement of one or more of the parathyroid glands causes autonomous overproduction of the parathyroid hormone (PTH), which leads to high serum calcium levels. **Objective:** The objective of this study was to compare the clinical, laboratory, and operative variables between premenopausal (pre-M) and postmenopausal (post-M) women with PHPT. **Materials and Methods:** A retrospective analysis of the data of female patients who underwent surgery for PHPT at a single center, from January 2011 to December 2020, was done. Patients with familial PHPT and secondary hyperparathyroidism were not included. **Results:** Of the 130 women with PHPT, 44.6% were pre-M and 55.4% were post-M. A significantly higher number of pre-M females were symptomatic compared to post-M females (pre-M vs. post-M, 84.5% vs. 68.1%, $P = 0.031$). Renal calculi were more common in pre-M women (34.5% vs. 18.1%, $P = 0.032$), while the rest of the clinical features were comparable between the two groups. The proportion of women with osteoporosis (6.7% vs. 19.4%, $P = 0.071$), hypertension (13.8% vs. 34.7%, $P = 0.012$), and diabetes mellitus (3.5% vs. 16.7%, $P = 0.033$) was lesser in the pre-M group. Elevated serum alkaline phosphatase levels were significantly more prevalent in the pre-M group (37.9% vs. 20.8%, $P = 0.032$). The mean serum calcium (12.35 ± 1.28 vs. 11.96 ± 1.22 mg/dL, $P = 0.079$), median serum PTH (334 vs. 239 pg/mL, $P = 0.051$), and median weight of the operated adenomas (1.75 vs. 1.45 g, $P = 0.075$) were also higher in pre-M females. The proportion of ectopic adenomas and multiple adenomas, presurgery adenoma localization rates, and disease cure rates did not differ according to the menopausal status. The occurrence of postoperative hungry bone syndrome was higher in the pre-M women (15.5% vs. 1.4%, $P = 0.008$). **Conclusion:** The majority of women with PHPT are post-M, but symptomatic presentation is more common in pre-M females. The severity of the disease appears to be more in pre-M women; however, imaging and operative variables generally did not significantly differ between the two groups.

Keywords: *Hypercalcemia, menopause, parathyroid adenoma, primary hyperparathyroidism, renal calculi*

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder, characterized by autonomous production of the parathyroid hormone (PTH), which leads to hypercalcemia due to aggravated calcium

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Address for correspondence: Dr. Aasim N. Maldar, Veer Savarkar Road, Mahim, Mumbai - 400 016, Maharashtra, India.
E-mail: aasim.maldar@gmail.com

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resorption from the bones, and increased calcium reabsorption from the renal tubules.[1] PHPT patients in the Western countries are scarcely symptomatic, but in India, they often present with renal calculi, bone demineralization, fractures, weakness and fatigue, dyspepsia, pancreatitis, neuropsychiatric complaints, etc., though the incidence of asymptomatic presentation is lately increasing, probably due to preventive health checkups discovering hypercalcemia in the presymptomatic stage.[2-7]

The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons report the prevalence of PHPT to be around 1% in the adult population, increasing to 2% after the age of 55 years.[8] Women are two to three times more commonly diagnosed with PHPT as compared to men, and more-so in patients older than 50 years of age.[9,10] Thus, postmenopausal (post-M) women have the highest prevalence of PHPT. Several studies from India have also reported that PHPT is more common in women; however, it is usually diagnosed a decade earlier than in the Western population.[2,6,7,11-14] A recent study reported that in India, premenopausal (pre-M) patients were the dominant population with PHPT, as compared to post-M patients.[15]

To the best of our knowledge, only three studies worldwide have reported the effect of menopause on the presentation and severity of PHPT.[15-17] In the present study, we retrospectively evaluated differences in the clinical, laboratory, and surgical outcome data in female patients who were diagnosed with PHPT and underwent parathyroidectomy at our center, with respect to the menopausal status.

Materials and Methods

Evaluation of the retrospective data was performed from the electronic records of 222 patients with hyperparathyroidism, who underwent surgery between January 1, 2011, and December 31, 2020, at our center. Approval for the study was obtained from the institutional ethics committee.

Diagnosis of PHPT was established by the presence of hypercalcemia (albumin-adjusted serum calcium: >10.4 mg/dL) with inappropriately normal or elevated serum PTH levels (>25 pg/mL), or normocalcemic (albumin-adjusted serum calcium: 8 to 10.4 mg/dL) patients with elevated serum PTH (>72 pg/mL), after ruling out secondary causes of hyperparathyroidism. No patients had thiazide- or lithium-induced hypercalcemia, and familial hypocalciuric hypercalcemia (FHH) was excluded based on family history and a 24-h urine calcium excretion. Patients diagnosed with familial PHPT (n = 3) and secondary renal hyperparathyroidism (n = 19) were excluded from the current study. Out of the remaining 200 operated PHPT cases, 130 were women, who were included in the study.

Information related to the demographics, symptoms, comorbidities, menstrual history, laboratory parameters, imaging characteristics, surgical data, and outcomes of all the patients was collected by reviewing the individual case files electronically in the medical record section. The data were collated and tabulated, and the analysis and comparison were done between the pre-M and the post-M women. Menopause was defined clinically as the absence of menstruation for more than 1 year.[18]

Laboratory parameters such as serum calcium (normal range: 8 to 10.4 mg/dL, Arsenazo III method), inorganic phosphate (normal range: 2.5 to 5 mg/dL, phosphomolybdate method), albumin (normal range: 3.5 to 5 g/dL, bromocresol green method), and creatinine (normal range: 0.5 to 1.1 mg/dL, modified Jaffe's method) were measured by an autoanalyzer (DXC 700 Chemistry Analyzer®, Beckman Coulter®, USA). Serum alkaline phosphatase (ALP) was measured by different methods using various buffer systems, with varying normal ranges, over the past decade. Hence, we categorized the levels as normal or high, rather than absolute numbers. The albumin-corrected calcium levels were calculated using the modified Payne formula, i.e. corrected calcium in mg/dL = measured total serum calcium in mg/dL + 0.8× (4.0 − patient's serum albumin concentration in g/dL). Quantitative titers for serum intact PTH levels (normal range: 12 to 72 pg/mL) were run on automated Siemens® Immulite® 2000, Germany, using solid-phase two-site chemiluminescent immunoassay (CLIA) method, with the intra- and inter-assay variability of less than 10%. 25-hydroxy Vitamin D (25OHD) titers were run on Liaison Analyzer® by DiaSorin®, Italy, using the flash CLIA method with a paramagnetic microparticle solid phase. Vitamin D deficiency was defined as a serum 25OHD <20 ng/mL.

The parathyroid lesion (s) was localized by neck ultrasonography, and/or dual-phase 99mTc-sestamibi scan with single-photon emission computed tomography–computed tomography (SPECT-CT), and/or contrast-enhanced CT scan. Ultrasonography was performed using a high-frequency linear probe (6–15 MHz), while the sestamibi scan was done using 20 mCi of 99mTc-sestamibi and obtaining images at 15, 30, 90, and 240 min. SPECT images were obtained for all the patients undergoing sestamibi scans. Osteitis fibrosa cystica (OFC) was identified on X-rays

of the affected region as a lytic lesion of varying sizes and shapes.

Histopathological confirmation of parathyroid adenoma or hyperplasia was done in all patients who underwent surgery. Indication for surgery in asymptomatic patients followed the third and fourth international workshop guidelines for the management of PHPT.[19,20] Cure was defined as the alleviation of hypercalcemia by the first postoperative follow-up. Based on the reference values of our laboratory, hungry bone syndrome (HBS) was defined by an albumin-corrected serum calcium <8 mg/dL and serum PTH ≥12 pg/mL, between postoperative days 4 and 7.

All analyses were performed using the Statistical Package for the Social Sciences®, Version 22.0, IBM Corp.®, Armonk, New York, USA. Variables were preliminarily tested for distribution with the Shapiro–Wilk W test. Normally distributed data were presented as mean ± standard deviation (SD) and were analyzed using the unpaired Student's *t*-test. Skewed data were presented as median with range, and were analyzed using the Mann–Whitney U test. Differences in categorical variables were analyzed by using the Chi-square test. Yates' correction was applied to the Chi-square test where one or more values were less than 10. Spearman coefficient was applied to evaluate the correlation between the weight of the adenoma and other variables such as the presence of symptoms, serum calcium, serum phosphorous, serum PTH, serum 25-OHD, and high serum ALP; multiple linear regression was applied for the correlating data. P <0.05 was considered statistically significant.

Results

Of the 130 female patients with PHPT, 58 (44.6%) were pre-M and 72 (55.4%) were post-M.

Clinical parameters

Thirty-two (24.6%) women were asymptomatic at presentation. Women most commonly presented with bone disease (74, 56.9%), followed by gastrointestinal conditions (53, 40.8%), weakness and fatigue (50, 38.5%), hypertension (33, 25.4%), and renal calculi (30, 23.1%). Proximal myopathy, neuropsychiatric complaints, and weight loss were seen in 10% or less of the patients [Table 1].

A higher number of post-M women were asymptomatic at presentation as compared to pre-M women (pre-M vs. post-M, 15.5% vs. 31.9%, P = 0.031). Renal calculi were more common in pre-M women (34.5% vs. 18.1%, P = 0.032), while hypertension (13.8% vs. 34.7%, P = 0.012) and diabetes (3.5% vs. 16.7%, P = 0.033) were more frequently seen in post-M women. Clinical parameters such as bone pains, OFC, dyspepsia, gallstone disease, pancreatitis, weakness-fatigue, neuropsychiatric manifestations, and weight loss were comparable between the two groups. Osteoporosis

Table 1: Comparison of clinical parameters between pre- and postmenopausal primary hyperparathyroidism patients

Parameter	Total (n=130), n (%)	Pre-M (n=58), n (%)	Post-M (n=72), n (%)	P
Mean age (years)	52.1±15.7	37.9±9.7	63.5±8.8	<0.001
Asymptomatic	32 (24.6)	9 (15.5)	23 (31.9)	0.031
Bone disease	74 (56.9)	32 (55.2)	42 (58.3)	0.718
Bone pains	43 (33.1)	21 (36.2)	22 (30.6)	0.496
Osteoporosis	18 (13.9)	4 (6.9)	14 (19.4)	0.071
Osteitis fibrosa cystica	7 (5.4)	4 (6.9)	3 (4.2)	0.768
Fracture	6 (4.6)	2 (3.5)	4 (5.6)	0.882
Gastrointestinal manifestations	53 (40.8)	29 (50)	24 (33.3)	0.055
Abdominal pain	18 (13.9)	12 (20.7)	6 (8.3)	0.076
Dyspepsia	11 (8.5)	6 (10.3)	5 (6.9)	0.707
Gallstone disease	15 (11.5)	6 (10.3)	9 (12.5)	0.915
Pancreatitis	9 (6.9)	5 (8.7)	4 (5.6)	0.695
Weakness and fatigue	50 (38.5)	24 (41.4)	26 (36.1)	0.54
Renal calculi	33 (25.4)	20 (34.5)	13 (18.1)	0.032
Hypertension	33 (25.4)	8 (13.8)	25 (34.7)	0.012
Proximal myopathy	13 (10)	8 (13.8)	5 (6.9)	0.317
Neuropsychiatric manifestations	4 (3.1)	2 (3.5)	2 (2.78)	0.771
Involuntary weight loss	3 (2.3)	2 (3.5)	1 (1.4)	0.849
Diabetes mellitus	14 (10.8)	2 (3.5)	12 (16.7)	0.033
Hypothyroidism	20 (15.4)	7 (12.1)	13 (18.1)	0.484
Ischemic heart disease	4 (3.1)	1 (1.7)	3 (4.2)	0.771

Pre-M: Premenopausal, Post-M: Postmenopausal

was seen more in post-M subjects (6.9% vs. 19.4%, $P = 0.071$), and abdominal pain was more common in pre-M subjects (20.7% vs. 8.3%, $P = 0.076$), but neither reached statistical significance [Table 1].

Laboratory parameters

A higher proportion of pre-M women had elevated serum ALP levels (37.9% vs. 20.8%, $P = 0.032$). The median serum PTH levels (334 vs. 239 pg/mL, $P = 0.051$) and the mean serum calcium levels (12.35 ± 1.28 vs. 11.96 ± 1.22, $P = 0.079$) were also higher in the pre-M group, than the post-M group, though they did not reach statistical significance. Serum phosphorous and serum 25OHD levels were similar between the two groups [Table 2].

Fifty-five (45.8%) women overall were Vitamin D deficient. Twenty-four (47.1%) pre-M and 31 (44.9%) post-M women were suffering from Vitamin D deficiency ($P = 0.817$).

Imaging, surgical, and postoperative parameters

Preoperative localization of the parathyroid adenomas was possible in 93.9% of females. Localization of parathyroid tumors, proportion of adenomas at the ectopic sites, and proportion of multiple adenomas were similar in both the groups. The median weight of adenoma was higher in the pre-M subjects (1.75 vs. 1.45 g, $P = 0.075$), but the postoperative remission rates were similar (89.7% vs. 94.4%, $P = 0.492$). Postoperative HBS was seen more commonly in the pre-M women (15.5% vs. 1.4%, $P = 0.008$) [Table 3].

Correlation of weight of adenoma with the studied parameters

The weight of the adenoma significantly positively correlated with serum PTH levels (R = 0.407, $P < 0.001$) and raised serum ALP (R = 0.309, $P = 0.001$); and it significantly negatively correlated to serum 25OHD levels (R = −0.255, $P = 0.011$). There was no significant correlation of adenoma weight with the presence of symptoms, serum calcium levels, serum phosphorous levels, and incidence of postsurgical HBS [Table 4]. By applying linear regression for the studied parameters, only serum PTH independently positively correlated with the weight of the adenoma (unstandardized coefficient = 0.001, standard error <0.001, $P = 0.036$).

Discussion

We observed that among the women with PHPT, a higher proportion is post-M (55.4%). This finding corroborates with the reports from other countries, where post-M women comprise the majority of PHPT cases.[16,17,21-24] One of the postulations is that the decline in estrogen levels after menopause may contribute to parathyroid tumorigenesis.[25,26] Estrogen deprivation also leads to osteoporosis in menopausal women, the evaluation

Table 2: Comparison of biochemical parameters between pre- and postmenopausal primary hyperparathyroidism patients

Parameter	Total (*n*=130)	Pre-M (*n*=58)	Post-M (*n*=72)	*P*
Mean serum calcium (mg/dL)	12.13±1.27	12.35±1.28	11.96±1.22	0.079
Mean serum phosphorous (mg/dL)	2.5±0.61	2.42±0.54	2.56±0.66	0.195
Median serum 25OHD (ng/mL)*	22 (1.5–89)	21 (1.5–89)	22 (3.9–67.2)	0.322
Median plasma PTH (pg/mL)	262 (42.7–3361)	334 (44.6–2500)	239 (42.7–3361)	0.051
Elevated serum ALP, *n* (%)	37 (28.5)	22 (37.9)	15 (20.8)	0.032
Mean serum creatinine (mg/dL)	0.88±0.3	0.75±0.22	0.98±0.31	<0.001

*Serum 25OHD levels were available for 120 patients (51 – pre-M and 69 – post-M). 25OHD: 25-hydroxy Vitamin D, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, Pre-M: Premenopausal, Post-M: Postmenopausal

Table 3: Comparison of imaging, operative, and postsurgery parameters between pre- and postmenopausal primary hyperparathyroidism patients

Parameter	Total (*n*=130), *n* (%)	Pre-M (*n*=58), *n* (%)	Post-M (*n*=72), *n* (%)	*P*
Localized presurgery*	122 (93.9)	54 (93.1)	68 (94.4)	0.96
Ectopic adenomas	5 (3.9)	3 (5.2)	2 (2.8)	0.805
Multiple adenomas	12 (9.2)	3 (5.2)	7 (9.7)	0.524
Median weight of adenoma (g)†	1.63 (0.4–10.4)	1.75 (0.6–9.1)	1.45 (0.4–10.4)	0.075
Hyperplasia	8 (6.2)	4 (6.9)	4 (5.6)	0.96
Postsurgery remission	120 (92.3)	52 (89.7)	68 (94.4)	0.492
Postsurgery HBS	10 (7.7)	9 (15.5)	1 (1.4)	0.008

*Localization with ultrasonography, and/or dual-phase ^{99m}Tc-sestamibi scan with SPECT-CT, and/or contrast-enhanced CT scan, †Adenoma weights were available for 109 patients (47 – pre-M and 62 – post-M). HBS: Hungry bone syndrome, Pre-M: Premenopausal, Post-M: Postmenopausal

Table 4: Correlation between weight of adenoma and the studied parameters

Variable	Weight of the adenoma (g)	
	R	*P*
Presence of symptoms	−0.078	0.426
Serum calcium (mg/dL)	0.16	0.1
Serum PTH (pg/mL)	0.407	<0.001
Serum phosphorous (mg/dL)	−0.178	0.067
Raised serum ALP	0.309	0.001
Serum 25OHD	−0.255	0.011
Postsurgery HBS	0.110	0.261

25OHD: 25-hydroxy Vitamin D, ALP: Alkaline phosphatase, HBS: Hungry bone syndrome, PTH: Parathyroid hormone, *R*: Spearman coefficient

of which may lead to the discovery of the underlying PHPT.[16] It has also been suggested that older women are more likely to be on thiazides (for hypertension) and Vitamin D-calcium supplementation (for osteoporosis prevention or treatment), which may elevate serum calcium, and while in the majority of cases, this creates false-positive diagnosis of PHPT, in some cases, they may actually unmask PHPT.[10,27] Furthermore, elderly women are likely to undergo comprehensive preventive health checkups more often, which may lead to the discovery of asymptomatic hypercalcemia. The prevalence of asymptomatic hypercalcemia and osteoporosis is higher in post-M women in our study.

The Indian PHPT Registry study by Arya *et al*. had contrarily reported that the majority (65.5%) of Indian women with PHPT were pre-M.[15] However, an interesting finding of this study was that the rate of increase in the total number of registrations was greater for post-M women over 5-year clusters from 2005 to 2019.[15] Overall, post-M patients increased 3.2-times compared to only 2.5-times increase in pre-M PHPT patients during the year 2015–2019, as compared to 2005–2009.[15] Meng *et al*. in their multicenter study reported a higher proportion of pre-M women from their Chinese center than the American center (37.9% vs. 21.5%), though post-M women were a majority at both the centers.[17]

Studies from India and developing nations have reported that the presentation of PHPT in these countries is at a younger age, with a higher symptomatic presentation, as compared to the USA and the European nations, but the trend in these countries, including India, is changing in the recent years, with an increasing prevalence of PHPT, and more elderly and asymptomatic patients being diagnosed with PHPT, as compared to earlier.[2,4-7,11-14,28-35] These trends indicate that the presentation of PHPT in India and the Eastern countries is changing to resemble more like the Western presentation, wherein more patients with PHPT are being diagnosed in the initial asymptomatic stage and later in life, unlike earlier when the diagnosis was only made after the patients developed an overt disease with symptoms of renal calculi, fractures, bone lesions, etc., The proportion of post-M women among females with PHPT as reported in the Indian PHPT Registry study by Arya *et al*. was 34.5%, our study was 55.4%, Meng *et al*. in their Chinese and American arms was 62.1% and 78.5%, respectively, and the Italian study was 83.3%.[15-17] Thus, our study done among the urban population of a metropolis may be an indicator of the transitioning of the PHPT profile to mimic more like the Western profile.

There are only three other studies that have reported the effect of menopause on the presentation of PHPT.[15-17] The clinical, laboratory, and surgical parameters reported by the studies are tabulated in Table 5.

In our study, significantly more pre-M women were symptomatic (84.5% vs. 68.1%, $P = 0.031$), with a higher prevalence of renal stone disease (34.5% vs. 18.1%, $P = 0.032$), as compared to post-M women. The prevalence of OFCs was not statistically different between the two groups in our study (6.9% vs. 4.2%, $P = 0.768$). Castellano *et al*. reported that symptomatic PHPT (64.8% vs. 43.3%, $P < 0.001$) and nephrolithiasis (59.2 vs. 28.1%, $P < 0.001$) were significantly more prevalent in pre-M women, while the presence of OFCs was higher in the post-M group (12.9% vs. 22.2%, $P = 0.308$).[16] Meng *et al*. reported a significantly higher prevalence of renal stone disease in pre-M women from their American center (29% vs. 26%, $P < 0.05$).[17] Arya *et al*. in their study reported that OFCs were more frequently observed in pre-M than in post-M subjects (23% vs. 14%, $P = 0.03$), while renal manifestations (52% vs. 46%, $P = 0.24$) were comparable between the two groups.[15] Thus, while all the studies report that symptomatic presentation is more common in the pre-M women as compared to post-M women, the Western studies and our study show that pre-M women have higher renal manifestations, and the Indian PHPT Registry study shows that pre-M women have higher skeletal manifestations (in the form of OFCs). In these studies, however, the higher prevalence of OFCs was seen to be associated with a higher prevalence of 25OHD deficiency – the pre-M group of Arya *et al*. (45% vs. 58%, $P = 0.03$) as well as the post-M group of Castellano *et al*.(30.5% vs. 38.9%, $P = 0.27$).[15,16] Bone disease is seen more commonly in South Asian and Middle-Eastern countries where 25OHD deficiency is common, as compared to Western countries, and an association between higher prevalence of bone disease

Table 5: Comparison of different studies for pre- and postmenopausal primary hyperparathyroidism women

Menopause status	Author, Country											
	Castellano *et al.*, Italy, 2017[16]		Meng *et al.*, USA, 2018[17]		Meng *et al.*, China, 2018[17]		Arya *et al.*, India, 2019 (Indian PHPT registry)[15]		Current study, India	
	Study period									
	January 1998–December 2016		2010–2016		2010–2016		2005–2019		January 2011–December 2020	
	Pre-M	Post-M	Pre-M	Post-M	Pre-M	Post-M	Pre-M	Post-M	Pre-M	Post-M
n (%)	54 (16.7)	270 (83.3)	28 (21.5)	102 (78.5)	33 (37.9)	54 (62.1)	232 (65.5)	122 (34.5)	58 (44.6)	72 (55.4)
Age (years)	40.5±8	65.9±8.7*	39.4±8.7	63.3±8.6*	38.7±9.7	63.2±7.6*	NA	NA	37.9±9.7	63.5±8.8*
Symptomatic, *n* (%)	35 (64.8)*	117 (43.3)	NA	NA	NA	NA	213 (91.8)	104 (85.2)	49 (84.5)*	49 (68.1)
Serum calcium (mg/dL)	11.2±1	11.2±1.2	11.2±0.6	11±0.5	13.4±2.7*	12.8±2.2	12.1±1.6	11.7±1.43	12.35±1.28	11.96±1.22
Serum phosphorous (mg/dL)	2.54±0.6	2.71±0.6*	NA	NA	NA	NA	2.56±0.6	2.65±0.58	2.42±0.54	2.56±0.66
Serum PTH (pg/mL), *n* (%)	126.5 (96.8)	139 (137)	170.3±156.5*	122.8±58.5	801.9±637.6*	503.2±516.7	403 (180–1015)*	246 (147–695)	334 (44.6–2500)	239 (42.7–3361)
Serum 25OHD (ng/mL)	31.8±21.6	28.1±20.3	26.7±12.7	30.8±10.9	13.9±7.3	14.2±8.3	20±13.8	27.1±18.1*	21 (1.5–382)	22 (3.9–67.2)
Serum ALP (IU/L)	NA	NA	92.3±42.2	83.2±25.1	794±1034.3*	166.1±234.2	202 (125–612)*	145 (111–283)	NA	NA
Presurgery localization, *n* (%)	42 (77.7)	190 (70.4)	NA	NA	NA	NA	224 (96.5)	114 (93.4)	54 (93.1)	68 (94.4)
Tumor weight (g)	NA	NA	NA	NA	NA	NA	2.46 (1–6.6)	1.9 (0.78–3.98)	1.75 (0.6–9.1)	1.45 (0.4–10.4)

*Data between groups are statistically significant. 25OHD: 25-hydroxy Vitamin D, ALP: Alkaline phosphatase, NA: Not available, PTH: Parathyroid hormone, Pre-M: Premenopausal, Post-M: Postmenopausal, PHPT: Primary hyperparathyroidism

and low 25OHD levels in PHPT patients has been demonstrated in many studies previously.[6,7,14,15,30,32,36]

Pre-M women in our study had a significantly higher proportion of raised ALP levels (37.9% vs. 20.8%, $P = 0.032$), and also demonstrated higher calcium (12.35 ± 1.28 vs. 11.96 ± 1.22 mg/dL, $P = 0.079$) and PTH levels (334 vs. 239 pg/mL, $P = 0.051$), and higher adenoma weights (1.75 vs. 1.45 g, $P = 0.075$). Castellano *et al*. have reported that serum phosphorous levels were lower in pre-M as compared to post-M women (2.54 ± 0.6 vs. 2.71 ± 0.6 mg/dL, $P < 0.05$).[16] Pre-M women from the Chinese arm of Meng *et al*.'s study had significantly higher serum calcium (13.4 + 2.7 vs. 12.8 + 2.2 mg/dL, $P < 0.05$), PTH (801.9 + 637.6 vs. 503.2 + 516.7 pg/mL, $P < 0.05$), and ALP (794 + 1034.3 vs. 166.1 + 234.2 IU/L, $P < 0.05$) levels, while pre-M women from their American arm had significantly higher PTH levels (170.3 + 156.5 vs. 122.8 + 58.5 pg/mL, $P < 0.05$), as compared to post-M women.[17] Arya *et al*. also reported higher serum calcium (12.1 ± 1.6 vs. 11.7 ± 1.43 mg/dL, $P = 0.05$), PTH (403 vs. 246 pg/mL, $P = 0.02$) and ALP (202 vs. 145 IU/L, $P = 0.02$) levels, and higher adenoma weights (2.46 vs. 1.9 g, $P = 0.12$) in the pre-M group.[15] Thus, pre-M women, irrespective of the geographical location, have a more severe PHPT. A potential reason for this finding could be the selection bias of the studies where-in majority of the younger, pre-M women visit the clinic for various symptoms, while the majority of asymptomatic post-M women are more likely to be diagnosed with hypercalcemia incidentally by the use of multichannel chemistry screening tests.

We observed that postoperative HBS was seen more commonly in pre-M women (15.5% vs. 1.4%, $P = 0.008$). No studies have compared HBS with respect to the menopausal state; however, a study in PHPT patients has reported that patients who developed postsurgery HBS had higher presurgery PTH and ALP levels, and heavier parathyroid glands.[37] Arya *et al*. and Castellano *et al*. have reported similar adenoma localization rates in pre-M and post-M women.[15,16] One year after parathyroidectomy, 4.0% of pre-M and 1.8% of post-M PHPT patients had a persistent disease ($P = 0.27$) in the cohort studied by Arya *et al*.[15]

In our study, on correlational analysis, the weight of the adenoma positively correlated with serum PTH levels ($R = 0.407$, $P < 0.001$) and raised serum ALP ($R = 0.309$, $P = 0.001$), while it negatively correlated to serum 25OHD levels ($R = -0.255$, $P = 0.011$). Arya *et al*. found that serum calcium ($R = 0.268$, $P < 0.001$), PTH level ($R = 0.516$, $P < 0.001$), and ALP level ($R = 0.335$, $P < 0.001$) positively correlated with tumor weight.[15] Similarly, a significant correlation

between adenoma weight, serum calcium, and parathormone levels has been reported by a couple of other studies.[38,39]

Conclusion

Among the women with PHPT from our center, the majority are post-M; however, pre-M women more often present with symptoms, and renal stone disease. The severity of PHPT also appears to be more in pre-M women with higher serum calcium, PTH, and ALP levels, and heavier parathyroid glands. Importantly, the adenoma localization and surgical outcomes are equivalent between pre-M and post-M women, though postoperative HBS is more likely to occur in pre-M women. Hyperparathyroidism may be diagnosed early by raising greater awareness and screening of serum calcium levels in menopausal women, as they tend to have a milder disease.

Ours is a single-center retrospective study, lacking data on the clinical improvement, long-term cure rates, relapse of hyperparathyroidism, and mortality. Our study may also suffer from the selection bias, which can act as a limitation for the subgroup analysis. Prospective studies are needed to assess the direct effect of menopause on hyperparathyroidism presentation, severity, and progression.

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Conflicts of interest

There are no conflicts of interest.

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