7-1-2021

Differences in Primary Hyperparathyroidism Between Pre- and Postmenopausal Women in India

Ashutosh Kumar Arya

Sanjay Kumar Bhadada

Poonam Kumari

Kanhaiya Agrawal

Satinath Mukhopadhyay

See next page for additional authors

Recommended Citation

Arya AK, Bhadada SK, Kumari P, Agrawal K, Mukhopadhyay S, Sarma D, and Rao SD. Differences in Primary Hyperparathyroidism Between Pre- and Postmenopausal Women in India. Endocr Pract 2021; 27(7):710-715.

Authors

Ashutosh Kumar Arya, Sanjay Kumar Bhadada, Poonam Kumari, Kanhaiya Agrawal, Satinath Mukhopadhyay, Dipti Sarma, and Sudhaker D. Rao

Endocrine Practice 27 (2021) 710–715

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Original Article

Differences in Primary Hyperparathyroidism Between Pre- and Postmenopausal Women in India

Ashutosh Kumar Arya, PhD [1], Sanjay Kumar Bhadada, MD, DM [1,*], Poonam Kumari, MSc [1], Kanhaiya Agrawal, MD [1], Satinath Mukhopadhyay, MD, DM [2], Dipti Sarma, MD [3], Sudhaker D. Rao, MD [4]

[1] *Departments of Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India*
[2] *Endocrinology & Metabolism, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India*
[3] *Gauhati Medical College and Hospital, Guwahati, Assam, India*
[4] *Bone and Mineral Research Laboratory, Henry Ford Hospital, Detroit, USA*

ARTICLE INFO

Article history:
Received 18 December 2020
Accepted 21 December 2020
Available online 29 December 2020

Key words:
primary hyperparathyroidism
menopause
PHPT registry

ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is a common endocrine disorder in women which becomes more prevalent after menopause. In this study, we compared the demographic, clinical, and biochemical variables between premenopausal (pre-M) and postmenopausal (post-M) women with PHPT.

Methods: A retrospective analysis (from 2005 to 2019) of enrolled women PHPT patients from an online Indian PHPT registry.

Results: Of the women with PHPT, 232 and 122 were pre-M and post-M, respectively. The number of post-M PHPT cases registered had a 3.3-fold increase in 2015-2019 from 2005-2009 compared with only a 2.5-fold increase in pre-M cases in the same duration. The majority were symptomatic (90%), although pre-M had a higher proportion of symptomatic than post-M (92% vs 85%; $P = .04$). Pre-M women showed more prevalence of osteitis fibrosa cystica than post-M women (28% vs 13%; $P = .03$), although hypertension and gallstone disease were seen more frequently in post-M PHPT women. Pre-M women had a significantly higher median PTH (403 vs 246 pg/mL; $P = .02$) and median alkaline phosphatase (202 vs 145 pg/mL; $P = .02$) than post-M women, and vitamin D deficiency was more common in pre-M women (58% vs 45%; $P = .03$). Gland localization, tumor weight, and disease cure rates did not differ according to menopausal status.

Conclusion: PHPT was more prevalent in pre-M women, although the number of post-M cases had significantly increased in the last 10 years. Pre-M women had generally more severe clinical and biochemical variables than post-M PHPT women.

Introduction

Primary hyperparathyroidism (PHPT) is a systemic disease characterized by hypercalcemia and an excessive secretion of parathyroid hormone (PTH).[1] Its clinical presentation in Western countries is mostly asymptomatic probably because of the routine use of multichannel chemistry picking up most patients in the presymptomatic stage. However, in the Indian subcontinent, the disease is still predominantly diagnosed with moderate to severe clinical symptoms, with bone disease, renal involvement, weakness and fatigue, gastrointestinal as well as neuropsychiatric symptoms.[2-6]

Women worldwide are approximately 3 times more frequently affected by PHPT than men. In Western populations, postmenopausal (post-M) women make a significant proportion of PHPT patients. However, in India, PHPT is often diagnosed at a younger age than their Western counterparts.[6-10] Only a handful of

Abbreviations: ALP, alanine phosphatase; BMI, body mass index; iPTH, intact parathyroid hormone; OFC, osteitis fibrosa cystica; PHPT, primary hyperparathyroidism; post-M, postmenopausal; pre-M, premenopausal; PTH, parathyroid hormone; 25-OHD, 25-hydroxyvitamin D.

* Address correspondence and reprint requests to Dr Sanjay Kumar Bhadada, Professor, Department of Endocrinology Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India.
E-mail address: bhadadask@rediffmail.com (S.K. Bhadada).

https://doi.org/10.1016/j.eprac.2020.12.012
1530-891X/

studies have evaluated the difference in the disease based on gender. Renal stones appear to be more common in men and bone disease more common in women.[11-14] To the best of our knowledge, only 2 studies have explored the effect of menopause on the presentation of PHPT.[15,16] Castellano et al[15] reported that premenopausal (pre-M) women had a higher frequency of renal stones and more clinical symptoms than post-M women with PHPT. Meng et al[16] found that post-M women in the USA had a higher prevalence of PHPT than those in China.

In the current study, we evaluated the changing trend of the demographic, clinical presentation, and biochemical profile of women with PHPT in the last 25 years from the Indian PHPT registry and compared these parameters between pre-M and post-M PHPT patients.

Methods

Subjects

The national online Indian PHPT registry (www.indianphptregistry.com) was started at the Department of Endocrinology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. The study was approved by the Institutional Ethics Committee of PGIMER, Chandigarh, India. PHPT patients only visiting PGIMER, Chandigarh center were included in the current study. Clinically suspected patients of PHPT and patients found to have hypercalcemia with high PTH during routine biochemical screening were evaluated, and confirmed PHPT patients were enrolled in the Indian PHPT registry. Written and informed consent was obtained from each study participant. The diagnosis of PHPT was established by the presence of hypercalcemia (albumin corrected serum calcium >10.2 mg/dL, at least twice 24 h apart) and inappropriately elevated PTH levels (> 65 pg/mL) or normocalcemic patients with elevated intact parathyroid hormone (iPTH) levels. Patients diagnosed with familial PHPT (n = 16) and secondary renal hyperparathyroidism (n = 23) were excluded from the current study. Of 472 PHPT cases, 354 were women. The demographic, clinical features, biochemical measurements, and postparathyroidectomy data were extracted from the registry, analyzed, and compared between pre-M and post-M women. Menopause was clinically defined as the absence of menstruation for more than 1 year.[17]

Demographic data extracted from the registry included age, height, weight, and body mass index (BMI). Radiographic evaluation performed by skeletal survey, looking for fracture, osteitis fibrosa cystica (OFC), subperiosteal resorption, and 'salt and pepper' appearance of the skull, were recorded. Renal manifestations were confirmed by the history of stone or using ultrasound or non-contrast computerized tomography of the kidney, ureter, and bladder for the presence of nephrolithiasis and/or nephrocalcinosis.

Biochemical parameters, such as serum calcium (RR, 8.6-10.2 mg/dL), inorganic phosphate (RR, 2.7-4.5 mg/dL), albumin (RR, 3.4-4.8 mg/dL), alkaline phosphatase (ALP) (RR, 40-129 IU/L), and creatinine (RR, 0.6-1.3 mg/dL), were measured by an autoanalyzer (Modular P800, Roche Diagnostics). Serum iPTH and 25-hydroxyvitamin D were measured by an electrochemiluminescence assay (Elecsys 2010, Roche Diagnostics). Vitamin D deficiency was defined as a serum 25-hydroxyvitamin D <20 ng/mL. Antibodies used in the PTH assay has <0.1% cross reactivity with osteocalcin, β-cross laps, bone specific ALP as well as PTH fragments PTH (1-34) and PTH (7-84).[18]

The parathyroid lesion was localized by neck ultrasonography and/or dual-phase (99m)Tc-sestamibi planar followed by surgery of imaging-confirmed cases with a histopathological confirmation of parathyroid adenoma/hyperplasia/carcinoma. After achieving a consistent normalization of serum calcium after surgery, patients were labeled as cured and all patients were supplemented with vitamin D. The decision of surgery for asymptomatic patient were based on the Third and Fourth International Workshop Guidelines for the management of PHPT.[19,20]

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences version 20. Variables were preliminarily tested for normal distribution using the Shapiro-Wilk W test. Normally distributed data were presented as mean ± SD, and skewed data were presented as median with interquartile range or otherwise, as described. Continuous variables with normal distribution were analyzed using the Student's *t* test, and skewed data were analyzed using the Mann-Whitney U test. Differences in categorical variables were analyzed using the chi-square test. Linear regression analysis was performed to correlate the biochemical factors, such as serum calcium, PTH, ALP, and 25-hydroxyvitamin D (25-OHD), with the adenoma weight. A P value < .05 was considered statistically significant.

Results

Of 405 women with PHPT recruited during 2005-2019 (15 years), 232 were pre-M (65.5%) and 122 (34.5%) were post-M. We evaluated the trend of pre-M and post-M registrations in 5-year clusters. The total number of registrations increased in each time period; however, the rate of increase was greater for post-M women. Therefore, the average age of registrants increased over time (Fig. 1). Overall, post-M patients showed a 3.2-fold increase compared with the only 2.5-fold increase in pre-M PHPT patients during the 2015-2019 compared with 2005-2009.

Comparison Between Pre-M and Post-M PHPT Patients

Demographic Features

The mean BMI was 24.4 ± 5.7 kg/m^2. Post-M women had a significantly higher BMI (25.5 ± 5.8 vs 23.9 ± 5.5 kg/m^2; P = .03) than pre-M women.

Clinical Features

Ninety percent (n = 317) had 1 or more clinical symptoms of PHPT, although there were more asymptomatic post-M women (15% vs 8%; P = .04). The most common clinical manifestation was bone disease (n = 213; 60%), followed by weakness and fatigue (n = 208; 59%), anemia (n = 200; 57%), renal manifestations (n = 177; 50%), hypertension (n = 122; 35%), abdominal pain (n = 96; 27%), gallstone disease (GSD) (n = 79; 22%), proximal myopathy (n = 49; 14%), and pancreatitis (n = 32; 9%).

Skeletal manifestations (bone pain, osteoporosis, fracture in long bones and spine or OFC) were observed in 141 (61%) of pre-M and 72 (59%) of post-M women. Pre-M women was observed to have a more frequent occurrence of OFC than post-M women (23% vs 14%; P = .03). Moreover, post-M PHPT women had a higher occurrence of hypertension (53% vs 25%; P < .0001) and GSD (28% vs 19%; P = 0.04) than pre-M PHPT women. However, other clinical parameters, such as weakness and fatigue (57% vs 62%; P = .33), renal manifestation (52% vs 46%; P = .24), anemia (59% vs 52%; P = .20), proximal myopathy (15% vs 13%; P = .49), pancreatitis (9.5% vs 8%; P = .82), and psychiatric manifestations (12% vs 10%; P = .68), were comparable between the 2 groups.

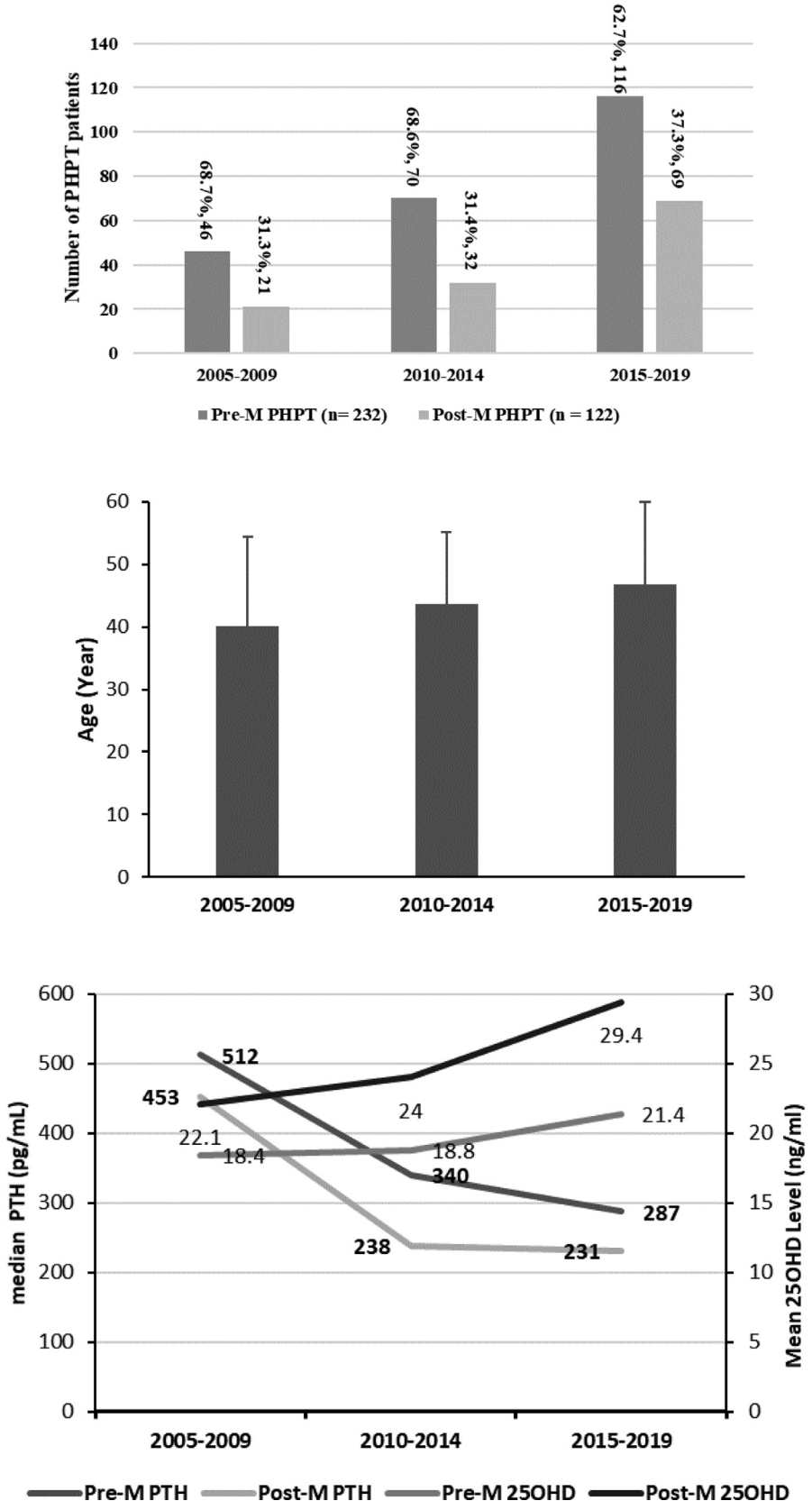

Fig. 1. Number of pre-M and post-M PHPT patients and trend of age, parathyroid hormone, and 25-hydroxyvitamin D levels in female PHPT patients in the last 15 years (2005-2019) (www.indianphptregistry.com).

Table 1
Comparison of Biochemical Parameters Between Premenopausal and Postmenopausal PHPT Patients

Parameters	Female PHPT (N = 354)	Premenopausal PHPT (n = 232)	Postmenopausal PHPT (n = 122)	*P* value
Serum calcium (8.6-10.2 mg/dL)	11.9 ± 1.54	12.1 ± 1.60	11.7 ± 1.43	.05
Serum phosphate (2.5 -4 mg/dL)	2.61 ± 0.61	2.56 ± 0.60	2.65 ± 0.58	.18
Serum alkaline phosphatase (40-129 IU/L) [a]	179 (119-501)	202 (125-612)	145 (111-283)	**.02**
Plasma iPTH (15-65 pg/mL)[a]	321 (168-916)	403 (180-1015)	246 (147-695)	**.02**
Plasma 25-hydroxyvitamin D (Vitamin D deficiency <20 ng/mL)	22.5 ± 15.8	20.0 ± 13.8	27.1 ± 18.1	**.0001**
Serum creatinine (0.5-1.2 mg/dL)	0.99 ± 0.61	0.92 ± 0.57	1.14 ± 0.65	**.002**
Urinary calcium (mg/24 h)	289.3 ± 268.9	294.4 ± 284.2	262.2 ± 250.3	.51
Preoperative localization, n (%)	338 (95.5%)	224 (96.5%)	114 (93.4%)	.87
Tumor weight (g)[a]	2.14 (0.85-5.50)	2.46 (1.0-6.6)	1.9 (0.78-3.98)	.12

Abbreviations: iPTH = intact parathyroid hormone, PHPT = primary hyperparathyroidism.
[a] Data was presented as median (interquartile range) and Mann-Whitney U test was used for comparison between the groups.

Biochemistry

Table 1 describes the biochemistry and hormonal profile of both groups. Pre-M PHPT women had significantly higher median plasma iPTH levels (403 [180-1015] vs 246 [147-695]; $P = .02$) and median serum ALP levels (202 [125-612] vs 145 [111-283]; $P = .02$) than post-M PHPT women. The mean values of serum albumin-adjusted calcium (12.1 ± 1.60 vs 11.7 ± 1.43 mg/dL; $P = .05$) was marginally higher in pre-M women. The data of 25-hydroxyvitamin D was only available for 220 pre-M and 115 post-M women. Post-M women had a significantly higher mean 25-hydroxyvitamin D level than pre-M PHPT women (27.1 ± 18.1 vs 20.0 ± 13.8 ng/mL; $P = .0001$). In addition, 45% (n = 52) of post-M patients were vitamin D deficient (25-hydroxyvitamin D level <20 ng/mL) compared with 58% (n = 127) of pre-M women ($P = .03$). In pre-M women, the mean plasma 25-hydroxyvitamin D levels progressively increased from 18.4 ng/mL in 2005-2009 to 21.4 ng/mL in 2015-2019. In post-M women, mean plasma 25-hydroxyvitamin D levels were higher, although showed a similar temporal trend increasing from 22.1 ng/mL in 2005-2009 to 29.4 ng/mL in 2015-2019. Overall, 25-hydroxyvitamin D levels significantly improved in the last 5 years (2014-2019) compared with the first cluster (2005-2009) in both groups at our center (Fig. 1).

In pre-M women, median iPTH levels showed a progressive decrease from 512 pg/mL in 2005-2009 to 287 pg/mL in 2015-2019. A similar temporal trend was seen in post-M registrants with a median iPTH decreasing from 453 pg/mL in 2005-2009 to 231 pg/mL in 2015-2019 (Fig. 1). We did not observe a significant change in other biochemical parameters over the time.

Post-M PHPT patients had a significantly higher mean serum creatinine levels than pre-M PHPT patients (1.14 ± 0.65 vs 0.92 ± 0.57 mg/dL; $P = .002$). No difference between pre-M and post-M women was observed in serum phosphate (2.56 ± 0.60 vs 2.65 ± 0.58 mg/dL; $P = .18$) (Table 1).

Postoperative Findings and Correlation of Tumor Weight With Disease Indices

Parathyroid tumors were localized in 338 (95.5%) subjects. Parathyroidectomy was performed if imaging was positive; the remainder (n = 16) were medically managed. The median duration of follow-up was 12 (6-36) and 12 (5-24) months, in the pre-M and post-M groups, respectively. The median tumor weight was higher in pre-M women (2.46 [1.0-6.6] vs 1.9 [0.78-3.98] g; $P = .12$). We correlated the log transformed serum Ca, PTH, ALP, and 25-OHD with the log transformed adenoma weight using a simple linear regression analysis. We found that the serum calcium ($r = 0.268$; $P < .0001$), PTH ($r = 0.516$; $P < .0001$), and ALP levels ($r = 0.335$; $P < .0001$) were positively correlated with the tumor weight. However, we did not observe a significant association between 25-hydroxyvitamin D and adenoma weight ($r = -0.065$, $P = .42$).

Histopathological findings were similar in the pre-M and post-M groups, with 340 (96%) having a single adenoma. One year after parathyroidectomy, 9 (4.0%) pre-M and 2 (1.8%) post-M PHPT patients had a persistent disease ($P = .27$).

Discussion

We observed that while pre-M women predominated in the registry, there was a distinct trend with an increasing number of post-M women being registered, thereby increasing the average age. Pre-M women had more severe bone disease and biochemical variables than post-M women. Parathyroidectomy cured the disease in both groups. These findings differ from reports from the USA and Europe, where post-M women comprise the majority (50%-70%) of PHPT cases,[8,21-23] and an estrogen deficiency might influence the difference in clinical presentation in post-M women. The estrogen deficiency in menopause plays a significant role in the development of osteoporosis which is typically diagnosed in post-M women and also contributes to the higher percentage of PHPT reported from Western populations. [15]

In a multicenter study (duration, 2010-2016), Meng et al[16] reported that the Chinese center (Changsha) had more symptomatic disease than the USA center (New Brunswick) and also showed that post-M women made up 41% of cases in Changsha and 58% at New Brunswick. Pre-M patients comprised 25% and 17% at the Changsha and New Brunswick centers, respectively. Studies from India and other Asian countries reported that overall PHPT patients were younger than the USA and European countries.[3,10,24] The trend is changing with the increasing prevalence of asymptomatic cases in China and Brazil.[2,25,26] Asymptomatic PHPT as well as patients with milder symptoms have progressively increased at our center and in the country in the last 10 years similarly in the line of other Asian countries; however, younger symptomatic PHPT patients remain more prevalent.[27-29] We found that pre-M comprised 51% of the total and 68% of female PHPT cases at our center. The potential reason for the higher prevalence of pre-M patients or overall young patients at our center is possibly due to the aggressive nature of the disease in this part of the world, which is further aggravated due to the associated severe vitamin D deficiency. The PHPT in India and other developing countries are severe and aggressive compared with Western populations. The majority of patients still present with severe bone and kidney disease, which was previously reported from the USA and European countries in the 1970s.[1,3,30] Eastern PHPT patients have a significantly higher resected tumor weight than Western PHPT patients. Molecular studies have also reported a significantly more dysregulation in Indian PHPT patients.[31-33] The second possible explanation of an aggressive disease is the delay in diagnosis; however, that is not supported by the literature, as in India, PHPT patients are diagnosed in the fourth

Table 2
Comparison of Different Studies for Premenopausal and Postmenopausal PHPT Patients

Author/Country	Proportion of female PHPT	Symptomatic percentage	Serum calcium (mg/dL)	PTH (pg/mL)	25-OHD (ng/ml)	Serum ALP (IU/L)
Castellano et al, 2017, Italy[15]	**Pre-M:** 54 (16.7%)	35 (64.8%)	11.2 ± 1.0	126.5 (96.8)	31.8 ± 21.6	**NA**
	Post-M: 270 (83.3%)	117 (43.3%)	11.2 ± 1.2	139 (137)	28.1 ± 20.3	**NA**
Meng et al, 2018, China[16]	**Pre-M:** 33 (37.9%)	**NA**	13.4 ± 2.7[a]	801.9 ± 637.6[a]	13.9 ± 7.3	794 ± 1034[a]
	Post-M: 54 (62.1%)	**NA**	12.8 ± 2.2	503.2 ± 516.7	14.2 ± 8.3	166 ± 234
Meng et al, 2018, USA[16]	**Pre-M:** 28 (21.5%)	**NA**	11.2 ± 0.6	170.3 ± 156.5	26.7 ± 12.7	92 ± 42
	Post-M: 102 (78.5%)	**NA**	11.0 ± 0.5	122.8 ± 58.5	30.8 ± 10.9	83 ± 25
India, 2020, (current study)	**Pre-M:** 232 (65.5%)	213/232 (91.8%)	12.1 ± 1.60	403 (180-1015) [a]	20.0 ± 13.8	202 (125-612) [a]
	Post-M: 122 (34.5%)	104/122 (85.2%)	11.7 ± 1.43	246 (147-695)	27.1 ± 18.1[a]	145 (111-283)

Abbreviations: ALP = alanine phosphatase; NA = not available, PHPT = primary hyperparathyroidism; post-M = postmenopausal; pre-M = premenopausal; PTH = parathyroid hormone; 25-OHD = 25-hydroxyvitamin D.
[a] Data between groups are statistically significant.

decade, whereas in the USA and European countries, patients are diagnosed in the sixth decade of life.[1,3,21]

Skeletal manifestations are more common in women, whereas renal manifestations are more common in men with PHPT.[11-14,34] In symptomatic patients' skeletal features include bone pain, skeletal deformities, and pathological fractures reported in 40%-70% of PHPT cases.[3,24-26] We found that pre-M women had more severe skeletal involvement (in the form of OFC) than post-M women. OFC is now rarely reported from the Western countries and China with the recent increase of asymptomatic cases.[25,35]. However, in developing countries like India, skeletal problems are still prevalent in individuals with PHPT.[3,11,36] Furthermore, we observed that pre-M PHPT patients had higher median PTH and ALP levels than post-M PHPT patients. The potential reason of the severe disease in pre-M women is multifactorial. One reason could be that the younger skeleton responds more to the changes in PTH and vitamin D levels. Same was also supported by the peak bone mass and bone turn over markers in the third to fourth decades of life in the Indian population due to higher bone formation.[37] The mean age of pre-M women in our cohort was 37 years. It might also lead to more bone involvement in pre-M women, higher ALP levels, and tumor weight. The second potential reason for the higher percentage of pre-M women at our center as well as others from the region could be selection bias as most patients are presented with symptoms; however, in Western populations, most patients are diagnosed during the routine biochemical screening. In recent times, the awareness of bone diseases increased in the Indian population, and routine biochemical screening significantly increased in an older population. The same is also evident in the study published by Mithal et al[29] that showed an increased prevalence of the asymptomatic disease.

Additionally, pre-M women have been observed to have more vitamin D deficiency than post-M women. Post-M PHPT patients have been observed to have higher 25-hydroxyvitamin D levels than pre-M PHPT patients, in parallel with a progressive decrease in iPTH levels. Higher 25-hydroxyvitamin D levels in post-M PHPT women might be due to the rising trend of vitamin D supplementation prescribed by physicians for better bone health and more sunlight exposure. Bandeira et al[38] revealed that patients with PHPT who had OFC were younger and had lower 25-hydroxyvitamin D levels than patients with renal stones or who were asymptomatic. Other studies from India and China have also observed that patients with severe bone disease had severe vitamin D deficiency.[30,39] In the 2-center study of Meng et al[16], pre-M women with PHPT had higher mean serum calcium and PTH levels and lower 25-hydroxyvitamin D levels than post-M women with PHPT at the Changsha (China) center, although no difference was observed at the New Brunswick (USA) center (Table 2).

We found that the menopause was not associated with the increased renal manifestations; the higher serum creatinine levels in post-M patients presumably reflect age-associated changes in renal function. Previous studies have found that 10%-60% of women with PHPT had renal manifestations.[11,14-16] Meng et al[16] also showed that renal stones were more frequent in men, although they did not observe any difference between pre- and post-M PHPT women. However, renal stones were shown to be significantly higher in Changsha (China) than New Brunswick (USA) (54% vs 27%). The findings of our study on the renal manifestations in PHPT are thus comparable to the report by Meng et al[16] from the Chinese center.

Furthermore, we have observed a higher rate of GSD in post-M women. Previous studies from our center and others showed that PHPT had a higher prevalence of GSD or cholelithiasis than the general population.[40-42] In general, women with older age are associated with a higher prevalence of GSD.[43] Therefore, these factors together with hypercalcemia and high PTH might lead to more GSD occurrence in post-M women with PHPT. However, the exact cause and effect relationship is not well established.

To the best of literature search, this is the first study to explore the effects of menopause on the disease presentation, biochemical variables, and severity in women with PHPT. The present study is a retrospective single-center study that may have patient selection bias; therefore, we need prospective multicenter study plans to evaluate the direct effect of menopause on the disease presentation and severity. Not all PHPT patients had DXA, and had they all had DXA, perhaps the prevalence of bone disease would be higher than reported in the current study.

In conclusion, in India, pre-M patients are the dominant population in PHPT; however, post-M PHPT patients are progressively and significantly increasing. Pre-M PHPT patients had more severe bone disease with the biochemically more aggressive disease than post-M PHPT patients.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Bilezikian JP, Cusano NE, Khan AA, Liu JM, Marcocci C, Bandeira F. Primary hyperparathyroidism. *Nat Rev Dis Primers*. 2016;2:16033.
2. Bandeira F, Griz L, Caldas G, Bandeira C, Freese E. From mild to severe primary hyperparathyroidism: the Brazilian experience. *Arq Bras Endocrinol Metabol*. 2006;50(4):657–663.
3. Bhadada SK, Arya AK, Mukhopadhyay S, et al. Primary hyperparathyroidism: insights from the Indian PHPT registry. *J Bone Miner Metab*. 2018;36(2):238–245.
4. Arya AK, Bhadada SK, Mukherjee S, et al. Frequency and predictors of pancreatitis in symptomatic primary hyperparathyroidism. *Indian J Med Res*. 2018;148(6):721–727.
5. Mukherjee S, Bhadada SK, Arya AK, et al. Primary hyperparathyroidism in the young: comparison with adult primary hyperparathyroidism. *Endocr Pract*. 2018;24(12):1051–1056.
6. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int*. 2017;28(1):1–19.
7. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3580–3594.
8. Silverberg SJ, Walker MD, Bilezikian JP. Asymptomatic primary hyperparathyroidism. *J Clin Densitom*. 2013;16(1):14–21.
9. Silverberg SJ, Bilezikian JP. The diagnosis and management of asymptomatic primary hyperparathyroidism. *Nat Clin Pract Endocrinol Metab*. 2006;2(9):494–503.
10. Mishra SK, Agarwal G, Kar DK, Gupta SK, Mithal A, Rastad J. Unique clinical characteristics of primary hyperparathyroidism in India. *Br J Surg*. 2001;88(5):708–714.
11. Shah VN, Bhadada SK, Bhansali A, Behera A, Mittal BR, Bhavin V. Influence of age and gender on presentation of symptomatic primary hyperparathyroidism. *J Postgrad Med*. 2012;58(2):107–111.
12. Lundgren E, Hagström EG, Lundin J, et al. Primary hyperparathyroidism revisited in menopausal women with serum calcium in the upper normal range at population-based screening 8 years ago. *World J Surg*. 2002;26(8):931–936.
13. Mazeh H, Sippel RS, Chen H. The role of gender in primary hyperparathyroidism: same disease, different presentation. *Ann Surg Oncol*. 2012;19(9):2958–2962.
14. Weber T, Hillenbrand A, Peth S, Hummel R. Symptoms of primary hyperparathyroidism in men and women: the same but different? *Visc Med*. 2020;36(1):41–47.
15. Castellano E, Attanasio R, Boriano A, et al. Sex difference in the clinical presentation of primary hyperparathyroidism: influence of menopausal status. *J Clin Endocrinol Metab*. 2017;102(11):4148–4152.
16. Meng L, Liu S, Al-Dayyeni A, Sheng Z, Zhou Z, Wang X. Comparison of initial clinical presentations between primary hyperparathyroidism patients from New Brunswick and Changsha. *Int J Endocrinol*. 2018;2018:6282687.
17. Hall JE. Endocrinology of the menopause. *Endocrinol Metab Clin North Am*. 2015;44(3):485–496.
18. Arya AK, Sachdeva N. Changes in plasma intact parathyroid hormone levels following 24-hour incubation at room temperature as determined by Roche electrochemiluminescence PTH immunoassay. *Clin Lab*. 2014;60(4):689–692.
19. Bilezikian JP, Khan AA, Potts JT. Third International Workshop on the Management of Asymptomatic Primary H. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. *J Clin Endocrinol Metab*. 2009;94(2):335–339.
20. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561–3569.
21. Minisola S, Cipriani C, Diacinti D, et al. Imaging of the parathyroid glands in primary hyperparathyroidism. *Eur J Endocrinol*. 2016;174(1):D1–8.
22. Wermers RA, Khosla S, Atkinson EJ, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006;21(1):171–177.
23. Castellano E, Tassone F, Attanasio R, Gianotti L, Pellegrino M, Borretta G. Mild primary hyperparathyroidism as defined in the Italian Society of Endocrinology's Consensus Statement: prevalence and clinical features. *J Endocrinol Invest*. 2016;39(3):349–354.
24. Jha S, Jayaraman M, Jha A, Jha R, Modi KD, Kelwadee JV. Primary hyperparathyroidism: a changing scenario in India. *Indian J Endocrinol Metab*. 2016;20(1):80–83.
25. Zhao L, Liu JM, He XY, et al. The changing clinical patterns of primary hyperparathyroidism in Chinese patients: data from 2000 to 2010 in a single clinical center. *J Clin Endocrinol Metab*. 2013;98(2):721–728.
26. Bandeira F, Cusano NE, Silva BC, et al. Bone disease in primary hyperparathyroidism. *Arq Bras Endocrinol Metabol*. 2014;58(5):553–561.
27. Arya AK, Kumari P, Bhadada SK, et al. Progressive rise in the prevalence of asymptomatic primary hyperparathyroidism in India: data from PHPT registry. *J Bone Miner Metab*. 2020. https://doi.org/10.1007/s00774-020-01142-w.
28. Agrawal K, Arya AK, Sood A, et al. A detailed appraisal of renal manifestations in primary hyperparathyroidism from Indian PHPT registry: before and after curative parathyroidectomy. *Clin Endocrinol (Oxf)*. 2021;94(3):371–376.
29. Mithal A, Kaur P, Singh VP, Sarin D, Rao DS. Asymptomatic primary hyperparathyroidism exists in North India: retrospective data from 2 tertiary care centers. *Endocr Pract*. 2015;21(6):581–585.
30. Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities–New York and Beijing. *Int J Fertil Womens Med*. 2000;45(2):158–165.
31. Arya AK, Bhadada SK, Singh P, et al. Promoter hypermethylation inactivates CDKN2A, CDKN2B, and RASSF1A genes in sporadic parathyroid adenomas. *Sci Rep*. 2017;7(1):3123.
32. Varshney S, Bhadada SK, Arya AK, et al. Changes in parathyroid proteome in patients with primary hyperparathyroidism due to sporadic parathyroid adenomas. *Clin Endocrinol (Oxf)*. 2014;81(4):614–620.
33. Varshney S, Bhadada SK, Saikia UN, et al. Simultaneous expression analysis of vitamin D receptor, calcium-sensing receptor, cyclin D1, and PTH in symptomatic primary hyperparathyroidism in Asian Indians. *Eur J Endocrinol*. 2013;169(1):109–116.
34. Lila AR, Sarathi V, Jagtap V, Bandgar T, Menon PS, Shah NS. Renal manifestations of primary hyperparathyroidism. *Indian J Endocrinol Metab*. 2012;16(2):258–262.
35. Sun B, Guo B, Wu B, et al. Characteristics, management, and outcome of primary hyperparathyroidism at a single clinical center from 2005 to 2016. *Osteoporos Int*. 2018;29(3):635–642.
36. Gopal RA, Acharya SV, Bandgar T, Menon PS, Dalvi AN, Shah NS. Clinical profile of primary hyperparathyroidism from western India: a single-center experience. *J Postgrad Med*. 2010;56(2):79–84.
37. Pal R, Aggarwal A, Singh T, et al. Diagnostic cut-offs, prevalence, and biochemical predictors of sarcopenia in healthy Indian adults: the Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES). *Eur Geriatr Med*. 2020;11(5):725–736.
38. Bandeira F, Caldas G, Freese E, Griz L, Faria M, Bandeira C. Relationship between serum vitamin d status and clinical manifestations of primary hyperparathyroidism. *Endocr Pract*. 2002;8(4):266–270.
39. Harinarayan CV, Gupta N, Kochupillai N. Vitamin D status in primary hyperparathyroidism in India. *Clin Endocrinol (Oxf)*. 1995;43(3):351–358.
40. Bhadada SK, Bhansali A, Shah VN, Behera A, Ravikiran M, Santosh R. High prevalence of cholelithiasis in primary hyperparathyroidism: a retrospective analysis of 120 cases. *Indian J Gastroenterol*. 2011;30(2):100–101.
41. Shah VN, Bhadada SK, Bhansali A, et al. Effect of gender, biochemical parameters, and parathyroid surgery on gastrointestinal manifestations of symptomatic primary hyperparathyroidism. *Indian J Med Res*. 2014;139(2):279–284.
42. Broulik PD, Haas T, Adámek S. Analysis of 645 patients with primary hyperparathyroidism with special references to cholelithiasis. *Intern Med*. 2005;44(9):917–921.
43. Singh V, Trikha B, Nain C, Singh K, Bose S. Epidemiology of gallstone disease in Chandigarh: a community-based study. *J Gastroenterol Hepatol*. 2001;16(5):560–563.