Hellenic Journal of Surgery (2019) **91**:5-6, 153-158

Primary Hyperparathyroidism in a Predominantly Vitamin D Deficient Population: A Single Center Experience

Parvez Mohi Ud Din Dar[1,4], Liaqat Ahmad Malik[2], Afshan Anjum Wani[2], Supreet Kaur[1], Sajid Mohammad Wani[3], Muneer A Wani[2], Shariq R Masoodi[4], Khursheed Alam Wani[2], Wani Naveed Gulshan[5]

Abstract

Background: Primary hyperparathyroidism (PHPT) has a variable clinical presentation. Symptomatic PHPT continues to be the predominant form of the disease in the Indian subcontinent, but a decreasing trend of symptomatic cases is observed, and increasing numbers of asymptomatic cases are now being diagnosed. In these cases, 25-hydroxy vitamin D [25(OH)D] shows no correlation with the serum levels of calcium and intact parathyroid hormone (iPTH).

Objective: To study the characteristics of patients with hyperparathyroidism and the relationship of 25(OH)D with the levels of calcium and iPTH.

Methods: A study was conducted with 78 consecutive patients diagnosed from 1996 to 2018 with PHPT, in whom the vitamin D status was investigated preoperatively.

Results: Of the 78 study subjects, 67 (85.7%) were females and 11 (14.2%) were males. Their age ranged from 16 to 70 years. Nephrolithiasis was the single most common presentation (44.3%) followed by bone pain (42.6%). Only 5% of the subjects were asymptomatic, with a decreasing trend of symptomatic cases and increasing number of asymptomatic cases with time. Their mean serum calcium level was 11.5±1.0 mg/dl, mean serum iPTH level 377±386.1 pg/ml, mean 25(OH)D level 37.2±58.1 ng/ml, while 48% of the patients were vitamin D deficient.

The serum levels of 25(OH)D showed no correlation with serum calcium and iPTH levels, whereas it showed a negative correlation with tumor size. Neck ultrasound (US) was indicative of parathyroid pathology and laterality in 89.8% and showed the exact site of the parathyroid pathology in 63.3%. Technetium^{99}sestamibi (MIBI) scan was indicative of parathyroid pathology (side accuracy) in 92.5% and showed the exact site in 85.7% of patients.

A single parathyroid gland was involved in 90% of study subjects, double glands in 8% and multiple glands/hyperplasia in 1.6%. Histopathological examination showed parathyroid adenoma in 86.3% and parathyroid hyperplasia in 7.8%. Temporary post-operative hypocalcemia was detected in 36% of the patients; the cure rate was 98.4%, without any operative mortality.

Conclusion: Primary hyperparathyroidism continues to be mainly a symptomatic disease in the Kashmir Valley. There is a decreasing trend of symptomatic cases and an increasing number of asymptomatic cases with time. The level of 25(OH)D has no correlation with serum calcium, iPTH or tumor size in these patients.

Key words: *Parathyroid gland; vitamin D; primary hyperparathyroidism; surgery*

[1]*Department of Trauma Surgery and Critical Care, All India Institute of Medical Sciences (AIIMS), New Delhi, India*

[2]*Department of General and Minimal Access Surgery*

[3]*Department of psychiatry*

[4]*Department of Endocrinology*

Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir, India

[5]*Department of Pathology, Government Medical College, Jammu, Jammu and Kashmir, India*

Corresponding author: Dar Parvez Mohi-Ud-Din
Department of Trauma Surgery and Critical Care,
All India Institute of Medical Sciences, New Delhi, India – 110029
e-mail: Drparvez84@gmail.com

Received Jan 15, 2020; Accepted Jan 16, 2020

Introduction

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder. The exact incidence of the disease is difficult to estimate, as most of the patients with the condition remain asymptomatic. In the western world, PHPT is usually an asymptomatic disease; the patients are usually elderly and without renal and skeletal manifestations [1,2]. In the developing world, the clinical manifestations and pathological characteristics of condition are the same with those seen in the west several decades ago. The patients present mostly at younger age, with skeletal, renal and gastrointestinal manifestations [3-8].

Vitamin D is an important nutritional factor determin-

ing parathyroid growth. The variety of skeletal manifestations in relation to vitamin D levels suggests the possibility of a more complex pathogenesis [9,10]. The diagnosis of PHPT is mainly made by measurement of biochemical markers, including the serum levels of calcium and intact parathyroid hormone (iPTH). Ultrasonography (US) and technetium^{99}sestamibi (MIBI) scan are the two most commonly used imaging investigations for localization of the site and determination of the size of the abnormal parathyroid gland.

The most common cause of PHPT is parathyroid adenoma (80-85%) followed by parathyroid hyperplasia (10-15%) and carcinoma (1-1.5%). The only definitive treatment of PHPT is surgery, which is recommended for symptomatic and in selected asymptomatic patients. The primary goal of surgery is to remove the abnormal hyperfunctioning parathyroid gland [11,12].

Materials and methods

This study was designed to review the presentation and clinical features of patients diagnosed with primary hyperparathyroidism, and the outcome of surgery. Another key objective of this study was to study the vitamin D status of patients diagnosed with PHPT.

The hospital-based study was carried out retrospectively and prospectively. During the time period from 1996 to 2018, 78 consecutive patients with PHPT who underwent surgery were included in the study. Evaluation of the patients for HPT included measurement of serum calcium, inorganic phosphate, alkaline phosphate (ALP), iPTH, 25-hydroxy-vitamin D [25(OH)D], serum albumin, 24-hour urinary calcium and 24-hour urinary creatinine. The reference range for serum calcium and phosphate were 8.5-10.5 mg/dl and 3.5-4.5 mg/dl, respectively. The corrected calcium was calculated according to the formula: calcium (mg/dl) + [4–albumin (g/dl)]. The reference range for iPTH was 14 to 72 pg/ml. The 25(OH)D level was measured by radioimmunoassay (Roche Electrochemiluminesence technology). 25 (OH) D deficiency was defined as a level <20 ng/ml, insufficiency as levels 20-30 ng/ml, and sufficiency as levels >30 ng/ml.

Patients with elevated serum iPTH and/or serum calcium were further evaluated by imaging with US of the neck and MIBI scan. A radiological survey of hands, skull, lumbar spine, pelvis and any other suspected or known site of fractures and brown tumors was made. US of the neck was performed, by a single experienced radiologist, with a high resolution linear array transducer of 7.5-10 MHz. For MIBI scan, ^{99m} Tc sestamibi was administered intravenously and images were obtained at 15 minutes, 90 minutes and 120 minutes. Scan images showing foci of retained radiotracer in the delayed image were defined as positive scan imaging.

In cases where the US neck and MIBI scans were not indicative or were doubtful, neck and chest computed tomography (CT) was done. All symptomatic and asymptomatic patients who were diagnosed with PHTH according to the criteria for surgery of the National Institute of Health (NIH) underwent surgery. In the majority of patients, the exact location of the abnormal parathyroid gland was confirmed preoperatively, and unilateral neck exploration was performed. In the patients in whom the exact location of the abnormal gland was doubtful, or multiple parathyroid glands were involved, bilateral neck exploration was performed and all parathyroid glands were examined. A therapeutically acceptable outcome was defined by normalization of the serum levels of calcium and iPTH.

Statistical analysis

Statistical Software Package for Social Science (SPSS) version 16 was used for data analysis. The data was first keyed in MS Excel © 2007 before converting to SPSS for analysis. The results were expressed as percentage (%) or mean and standard deviation (mean ± SD). Pearson's Chi-square method was used for comparison of proportions and percentages, and Student's t –test was used for comparison of continuous variables. ANOVA was used wherever needed. Where the data was not uniformly distributed a non-parametric, Mann-Whitney U test, Kolmogorov-Smirnov Z test or Krushal-Wallis H test was used. A p value of < 0.05 was taken as significant.

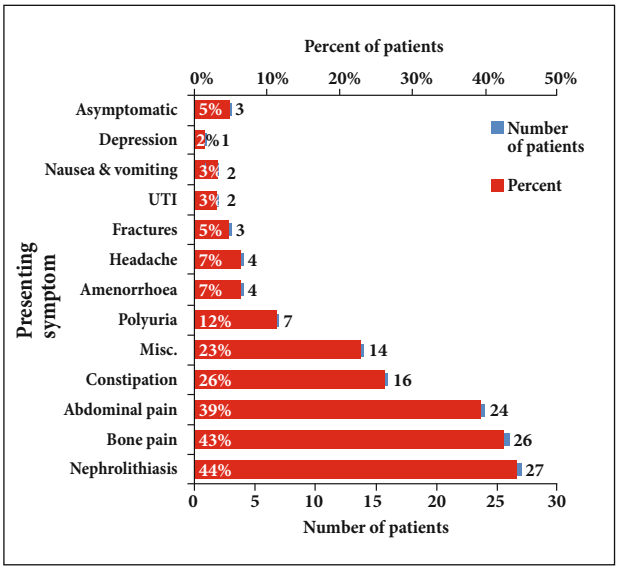

Figure 1. Presenting symptoms of primary hyperparathyroidism in the study subjects (N=78).

Results

A total of 78 patients were included in the study from 1996 to 2018, of which 67 (85.7%) were females and 11 (14.2%) were males with a male to female ratio of 1:6. Their age range was 16 to 70 years, mean 44.7±12.5 years, with no significant age difference between males and females. The presenting symptoms are shown in Figure 1. Most of the patients were symptomatic, with nephrolithiasis being the most common presenting symptom (44.3%) followed by bone pain (42.6%). Only 5% of the study subjects were asymptomatic.

The essential laboratory parameters in the study subjects are shown in Table 1. The mean serum calcium level of the study population was 11.5±1.0 mg/dl, and the mean serum iPTH level was 377±386.1 pg/ml. The vitamin D status in the patients is shown in Table 2, and the relationship of the Vitamin D status with preoperative and postoperative levels of calcium, iPTH and tumor volume in the study subjects is shown in Table 3.

A single parathyroid gland was involved in 90% of the patients, double glands in 8% and multiple/hyperplasia in 1.6%. The most common single gland was the right inferior (54%), followed by the left inferior (29%), right superior (6.6%), and multiple/ bilateral (9.8%). The histopathological examination showed parathyroid adenoma in 86.3%, and parathyroid hyperplasia in 7.8%. In 5.9% of the surgical samples the histopathology was inconclusive, but all the patients became asymptomatic, with serum calcium levels within the normal range after surgery.

The details about the accuracy of the preoperative imaging by neck US and MIBI scan (i.e., sensitivity, positive predictive value, likelihood of correct positive test and accuracy) are shown in Table 4.

The cure rate of the patients in this study was 98.4%. Temporary post-operative hypocalcemia was observed in 36% of the patients, which was symptomatic in 14.7%, and none developed permanent post-operative hypocalcemia. There were no operative deaths, and none of the patients presented vocal cord paralysis, surgical wound hematoma or surgical site infection.

Table 1. *The essential laboratory parameters in the study subjects with primary hyperparathyroidism (N=78).*

Laboratory parameters	Mean ±SD	Median	Range
iPTH (pg/ml)	377.6 ±386.1	224.5	70 – 1900
25-OH Vitamin D (ng/ml)	37.2 ±58.1	22.8	4.3 - 312.0
Serum Calcium (mg/dl)	11.5 ±1.0	11.3	9.1 - 15.6
ALP (U/L)	255.1±336.8	154.0	45 – 2476
Serum Phosphorus (mg/dl)	2.4 ±0.6	2.4	1.1 - 3.9

iPTH=intact parathyroid hormone

Table 2. *Vitamin D status of the patients with primary hyperparathyroidism (N=78).*

Vitamin D status [25(OH)D]	Percentage of study subjects
Deficient (<20 ng/ml)	48%
Insufficient (20 -30ng/ml)	21%
Normal (30 >100 ng/ml)	31%

Discussion

PHPT was considered to be a relatively rare, entity but with the advent of newer imaging modalities and calcium analyzers there has been an increase in its diagnosis. The exact incidence of the disease is difficult to estimate, since most of the patients remain asymptomatic. In the western world, PHPT is usually an asymptomatic disease; the patients are generally elderly and without renal and skeletal manifestations [1,2].

Table 3. *Relationship of Vitamin D status with preoperative (Pre-op) and postoperative (Post-op) levels of calcium, intact parathyroid hormone (iPTH) and tumor volume in the study subjects with primary hyperparathyroidism (N=78).*

Vitamin D status	**Median Pre-op. Calcium*** (mg/dl)	**Median Post-op. Calcium** (mg/dl)	**Median Pre-op. iPTH** (pg/ml)	**Median Tumour Size** (cc)
Deficient (<20 ng/ml)	10.9	8.9	236.5	1.0
Insufficient (20-30ng/ml)	10.5	9.2	147.0	0.6
Normal (30 >100 ng/ml)	10.8	9.1	245.6	0.8

Table 4. *Accuracy of preoperative imaging of the parathyroid glands, according to the histologic diagnosis of parathyroid adenoma/ hyperplasia (N=78).*

	Correct Side	Correct pole
USG		
– Sensitivity	89.8%	63.3%
– Positive predictive value	95.7%	96.9%
– Likelihood of correct positive test	0.9	1.3
– Accuracy	86.3%	62.7%
MIBI		
– Sensitivity	92.5%	85.7%
– Positive predictive value	96.1%	97.7%
– Likelihood of correct positive test	0.9	1.7
– Accuracy	89.1%	84.3%
Both USG & MIBI		
– Sensitivity	95.3%	88.4%
– Positive predictive value	97.6%	97.4%
– Likelihood of correct positive test	1.0	0.9
– Accuracy	93.2%	86.4%

USG=ultrasonography of the neck; MIBI=technetium99sestamibi scan

In our study the male to female ratio was 1:6. This female predominance was observed in both retrospective and prospective groups, and has been observed in all parathyroid lesions including parathyroid adenoma and parathyroid hyperplasia [14,15]. The age range of the patients, 16 to 70 years (mean 45 years) was similar to that in other reports [13]. Another recent study from India reported a mean age at presentation of 48 years [21]. Other studies, showed a shift in the presentation of PHPT from the 4th to the 5th decade of life in India, but most of our patients continue to be much younger than patients with PHPT from the western and other developed countries [9,22]. A possible reason for this early presentation in Indian patients could be an associated vitamin D deficiency [4,15].

In the developing world, the clinical manifestation and pathological characteristics of patients are the same with those observed in patients of western countries with predominant manifestation the young age and symptoms originating from the skeletal, renal and gastrointestinal systems [3-8]. In comparison with the western world and other developed countries, where most of the patients are asymptomatic, our study had the lowest percentage of asymptomatic patients (4.9%). The presentation of PHPT has changed over the years in developed countries, with a marked increase in number of patients with few or no symptoms. The reasons for this tendency may be related to the widespread use of screening tests, especially serum calcium measurement, in the developed part of world, and a reduction in vitamin D deficiency [18,19].

In our patients, the most common single presenting symptom was nephrolithiasis (44.3%) followed by bone pain (42.6%) and other symptoms, as shown Figure 1. Other Indian studies also reported nephrolithiasis in 31-70% of patients with PHPT [15,23-25]. The prevalence of renal stones in PHPT has dropped from 57% to <5% in the western world due to the detection of earlier and more asymptomatic cases [26].

Skeletal manifestation is the most common cause of morbidity associated with PHPT. Bhansali and colleagues reported bone disease in 67% of patients in their study [23]. Mishra and colleagues, in a study of 29 patients, found fractures in 57% and osteitis fibrosa cystica in all the patients [15]. Another recent study in India reported fractures in 25.8% of patients with PHPT and no brown tumors [27]. Skeletal manifestation was the second most common presentation in our patients, with bone pain being present in 43%, but fractures in only 5% and brown tumors in none. Our study patients showed the lowest number of fractures in any PHPT cohort from India, perhaps revealing a decreasing trend of skeletal manifestations of PHPT, which may be due to earlier diagnosis of the disease and improvement in the calcium and vitamin D nutrition of the population. Skeletal manifestations of PHPT in the west have declined from 23% to only 2% [10,28]. The difference in the skeletal manifestations of PHPT in western world and the Indian sub-continent is probably related to calcium and vitamin D nutrition, but other factors may also play a role [3].

PHPT may also present with other symptoms, including acute or chronic pancreatitis. The cause of pancreatitis in PHPT is the activation of trypsinogen to trypsin by hypercalcemia. The laboratory parameters in our patients, shown in table 1, were higher than in the studies previously conducted in India [24,29,30], whereas 48% of our patients had vitamin D deficiency. No correlation was demonstrated between the 25(OH)D levels and the parathyroid adenoma weight or the serum calcium and iPTH in our patients, in agreement with the findings of another recent study [21]. In addition, vitamin D deficiency may not be the only significant cause of bone disease in patients with PHPT, and other factors may play a role. Some studies have reported a correlation between the serum 25(OH)D level and parathyroid adenoma [9,10]

All the patients in our study underwent parathyroidectomy; 90.2% had a single parathyroid adenoma, double parathyroid adenoma was found in 8.2% and multiple

adenoma/hyperplasia in 1.6%. There was 96.15% cure rate similar to other studies that have shown a cure rate of 96%-100% [15,23]. The hungry bone syndrome (HBS) was present in 10.2% of our patients, compared with previous studies, which have shown HBS in 24-82% [23,24,31,32]. The reason for the low rate of HBS in our patients may be that we administered vitamin D preoperatively to all the patients with serum levels of 25(OH)D of less than 30ng/dl. The literature shows that the recurrence rate of PHPT after surgery ranges from zero to 41.6% [23,24,33]. The recurrence rate in our series was zero during a follow up period of 1-9 years.

Conclusion

In the Kashmir Valley PHPT continues to be a severe, symptomatic disorder with skeletal, muscular and renal manifestations presenting at a young age, but there appear to be a decreasing trend of symptomatic cases and increasing numbers of asymptomatic cases. Vitamin D level shows no correlation with serum calcium and iPTH or tumor size. The use of US of the neck in combination with MIBI scan plays important role in the detection of parathyroid gland pathology. Surgery is the treatment of choice for PHPT, and, when performed by an experienced surgeon cures about 99% of patients. Parathyroidectomy results in biochemical normalization including, the serum level of both serum calcium and iPTH.

Conflict of Interest: *The authors declare that they have no conflict of interest. They also state that they have full control of all primary data and that they agree to allow the journal to review their data if requested.*

References

1. Silverberg SJ, Bilezikian JP. Primary hyperparathyroidism: still evolving? J Bone Miner Res 1997;12:856-62.
2. Lundgren E, Rastad J, Thrufjell E, et al. Population-based screening for primary hyperparathyroidismwith serum calcium and parathyroid hormone values in menopausal women. Surgery 1997;121:287-94.
3. Mithal A, Agarwal G, Singh AK, et al. Severe bone disease in primary hyperparathyroidism in Indians: A re-ection of calcium and vitamin D nutritional status? J Bone Miner Res 1997;12(Suppl):522.
4. Harinarayan CV, Gupta N, Kochupillai N. Vitamin D status in primary hyperparathyroidism in India. Clin Endocrinol 1995;43:351-8.
5. Ingemansson SG, Hugosson CH, Woodhouse NJY. Vitamin D deficiency and hyperparathyroidism with severe bonedisease. World J Surg 1988;12:517-21.
6. Meng XW, Xing XP, Liu SQ, et al. The diagnosis of primary hyperparathyroidism - analysis of 134 cases. Acta Academiae Medicinae Sinicae 1994;16:13.
7. Cheung PS, Boey YH, Wang CC, et al. Primary hyperparathyroidism: Its clinical pattern and results of surgical treatment in Hong Kong Chinese. Surgery 1988;103:558-62.
8. Kulak CAM, Bandeira C, Voss D, et al. Marked improvement in bone mass after parathyroidectomy in osteitis ®brosa cystica. J Clin Endocrinol Metab 1998;83:732-5.
9. Rao DS. Role of vitamin D and calcium nutrition in parathyroid growth and disease expression. In: Mithal A, Rao DS, Zaidi M, editors. Metabolic Bone Disorders. Lucknow: Indian Society of Bone Mineral Research; c1998. p. 25-8.
10. Silverberg SJ, Shane E, Dempster DW, et al. The effects of vitamin D insuf®ciency in patients with primary hyperparathyroidism. Am J Med 1999;107:561-7.
11. Bilezikian JP, Khan AA, Potts JT Jr, Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009;94:335-9.
12. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism. N Engl J Med 2011;365:2389-97.
13. Ohe MN, Santos RO, Barros ER, et al. Changes in clinical and laboratory findings at the time of diagnosis of primary hyperparathyroidism in a University Hospital in São Paulo from 1985 to 2002. Braz J Med Biol Res 2005;38:1383-7.
14. 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;21:171-7.
15. Mishra SK, Agarwal G, Kar DK, et al. Unique clinical characteristics of primary hyperparathyroidism in India. British Journal of Surgery 2001;88:708-14.
16. Hauache OM, Amarante ECJ, Mendoza B, et al. Análiseclínica, laboratorial e achadoscirúrgicos de 28 casos de hiperparatiroidismoprimário. ArquivosBrasileiros de Endocrinologia e Metabologia 1995;39:157-62.
17. Bilezikian JP, Meng X, Shi Y, et al. Primary hyperparathyroidism in women: A tale of two cities: New York and Beijing. International Journal of Fertility and Women's Medicine 2000;45:158-65.
18. Silverberg SJ. Natural history of primary hyperparathyroidism. Endocrinol Metab Clin North Am 2000;29:451-64.
19. Eigelberger MS, Clark OH. Surgical approaches to primary hyperparathyroidism. Endocrinol Metab Clin North Am 2000;29:479-502.
20. Parmar Girish, M. Lala, M. Chadha, N. F. Shah, P. H. Chauhan. Study of Primary Hyperparathyroidism. Indian J Endocrinol Metab 2012;16(Suppl 2):S418-20.
21. Mithal A, Kaur P, Singh VP, et al. Asymptomatic primary hyperparathyroidism exists in North India: Retrospective data from 2 tertiary care centers. Endocr Pract 2015;21:581-5.
22. Parfitt AM, Rao DS, Kleerekoper M. Asymptomatic primary hyperparathyroidism discovered by multichannel biochemical screening: Clinical course and considerations bearing on the need for surgical intervention. J Bone Miner Res 1991;6 Suppl 2:S97-101.
23. Bhansali A, Masoodi SR, Reddy KS, et al. Primary hyper-

parathyroidism in North India: A description of 52 cases. Ann Saudi Med 2005;25:29-35.
24. Gopal RA, Acharya SV, Bandgar T, et al. Clinical profile of primary hyperparathyroidism from Western India: A single center experience. J Postgrad Med 2010;56:79-84.
25. Priya G, Jyotsna VP, Gupta N, et al. Clinical and laboratory profile of primary hyperparathyroidism in India. Postgrad Med J 2008;84:34-9.
26. Heath H 3rd. Clinical spectrum of primary hyperparathyroidism: Evolution with changes in medical practice and technology. J Bone Miner Res 1991;6 Suppl 2:S63-70.
27. Pradeep PV, Jayashree B, Mishra A, et al. Systematic review of primary hyperparathyroidism in India: The past, present, and the future trends. Int J Endocrinol [Internet] 2011:921814. Available from: https://www.hindawi.com/journals/ije/2011/921814/
28. Cope O. The study of hyperparathyroidism at the Massachusetts General Hospital. N Engl J Med 1966;274:1174-82.
29. AACE/AAES Task Force on Primary Hyperparathyroidism. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism. Endocr Pract 2005;11:49-54.
30. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235:665-70.
31. Soin AS, Gupta S, Kochupillai N, et al. Primary hyperparathyroidism – An Indian study. Indian J Cancer 1994;31:72-7.
32. Pradeep PV, Mishra A, Agarwal G, et al. Long-term outcome after parathyroidectomy in patients with advanced primary hyperparathyroidism and associated Vitamin D deficiency. World J Surg 2008;32:829-35.
33. Kapur MM, Agarwal MS, Gupta A, et al. Clinical & biochemical features of primary hyperparathyroidism. Indian J Med Res 1985;81:607-12.