

Primary Hyperparathyroidism in Iran: A Review

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Over the past half century, the pattern of clinical presentation of primary hyperparathyroidism (PHPT) has changed dramatically in Western countries; indeed it has evolved from a severe disease to an asymptomatic condition. The story is completely different in Eastern countries, where PHPT still presents with the traditional pattern of bones and stones. The aim of the present review is to analyze Iranian experiences in the clinical, biochemical, radiological, and pathological findings of PHPT and to compare these features with those of patients from developed and developing nations.

Materials & Methods: An extensive search of PHPT literature was carried out. Of the relevant publications from 1980-2006 (3 international, 3 local) five yielded compressive data in large series of Iranian patients. The information was evaluated, analyzed, summarized and compared to that of patients from other Eastern and Western countries.

Results: A total of 356 patients were included in these studies; there were 317 females and 49 males, age range 11 to 72 years, mean age 38.2 ± 12.4 years with a female to male ratio of 6.4 to 1. Most patients presented with advanced skeletal involvement. Nephrolithiasis was diagnosed in 14-47% patients. Majority of patients had high serum PTH and low serum phosphorus levels; nearly all displayed some radiological changes suggestive of hyperparathyroid bone disease. Osteoporosis, subperiosteal bone resorption, salt and pepper appearance, brown tumor and pathologic fractures were frequent x-ray findings. Single adenoma was discovered in

most patients. There were few cases with parathyroid carcinoma. Mean parathyroid gland weight, reported in 177 cases, was 4.1 grams, (range 0.8 - 25 grams).

Conclusion: PHPT is a severe, symptomatic disease with serious complications and high morbidity in Iran. Advanced skeletal disease is the most common pattern of presentation at a young age.

Key Words: Hyperparathyroidism, I.R. Iran, Developing countries

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Introduction

Primary Hyperparathyroidism (PHPT) is characterized by unregulated parathyroid hormone (PTH) secretion and resulting hypercalcemia. Excess PTH leads to the potential for major complications at the level of target tissues, mainly bones and kidneys.

Albright and Reifstein originally described primary hyperparathyroidism as a disease of "bones and stones". Osteitis fibrosa cystica reported to be the hallmark of hyperparathyroid bone disease and kidney disease, manifested by nephrolithiasis or rarely nephrocalcinosis, was present in more than three fourths of patients at the time of diagnosis.¹⁻⁴ In the West, the disease today bears little resemblance to the originally described severe disease of "bones and stones". Indeed PHPT has evolved over the last four decades from a severe disease to an asymptomatic condition or a disorder with more

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subtle manifestations (Table 1).⁵⁻⁹ Recent studies have shown that the incidence of renal disease has been reduced from almost 50%-70%, common in the past, to nearly 10% of patients currently.^{9,10} Likewise, ostei

tis fibrosa cystica, the classic presentation of skeletal involvement in PHPT has been declined sharply in its relative frequency (Table 1).⁵⁻¹¹

Table 1. Changing profile of primary hyperparathyroidism*

Symptomatology (%)	Study			
	Cope (1930-1965)	Heath et al. (1965-1974)	Mallette et al. (1965-1972)	Silverberg et al. (1984-1999)
Nephrolithiasis	57	51	37	17
Skeletal disease	23	10	14	1.4
Asymptomatic	0.6	18	22	80

* Reference No.9

The reason for this dramatic change in disease profile is almost certainly the improved diagnostic approaches. With the advent of the automated chemistry analyzers which routinely measure serum calcium level, the frequency of diagnosis of PHPT has increased dramatically, whereas the classic manifestations of the disease have become much less common.⁵⁻⁹ In essence, in the

West, symptomatic disease is today the exception rather than the rule, with nearly more than 80% of cases having no symptoms.⁹⁻¹¹ The story is completely different in hyperparathyroid patients from developing countries. There are clearly major differences between features of PHPT in patients from these countries and those of subjects reported from developed nations (Table 2).

Table 2. Comparison of relevant clinical manifestations of PHPT between the East and West*

Variable	West (historic)	West (contemporary)	East (historic and contemporary)	Iran
Bone disease	50-60%	10-20%	80-100%	60-100%
Osteitis fibrosa cystica	25-50%	<2%	>50%	>50%
Palpable brown tumors	Infrequent	Almost never	Frequent	Frequent
Fractures	Frequent	Infrequent	Frequent	Frequent
Nephrolithiasis	50-80%	5-20%	10-40%	14.5-47%
Nephrocalcinosis	5-10%	Almost never	5-10%	<5%

* Reference No. 51

The aim of this review is to analyze Iranian experiences on the clinical, biochemical radiological and pathological features of PHPT in the country and to compare these findings with those of patients from developed and other developing countries.

Materials and Methods

In an effort to obtain Iranian literature on the subject of PHPT, a search was carried out of multiple data sources including PubMed, Embase, Ovid Medline, Science direct (Elsevier) Scholar Google, ISI, Iranmedex (Farsi) and Irandoc (Farsi) from 1980-2006.

There were 6 published papers, three in English (in international journals) and three in Persian (local medical journals). Five of these studies contained comprehensive information regarding demographic, clinical, laboratory, radiological, and pathological findings in relatively large series of Iranian patients;¹²⁻¹⁶ the information was evaluated, recorded, analyzed and compared to that of

patients from the Eastern and Western countries.

Results

A total of 356 patients were included in these studies. Demographic, clinical, biochemical, radiological findings and parathyroid gland weights have been recorded in Tables 3 and 4.

Table 3. Results of published studies in PHPT patients from Iran

Parameter	Study				
	Bahrami Tabriz (15)*	Atefi Shiraz(14)*	Ghazi Tehran(12)*	Nakhjavani Tehran(13)*	Hamidi Tehran (16)*
Time period	1985-2002	1981-2000	1987-1993	1989-1998	1981-2003
No. of patients	62	40	30	47	177
Female to male ratio	5:1	9:1	5:1	15:1	5.5:1
Mean age of patients (y)	38.6	34	36.2	38	42
Most common form of presentation	skeletal	skeletal	skeletal	skeletal	-
Bone disease (%)	93.5%	100%	100%	60%	-
Renal disease (%)	14.5%	22.5%	47%	17%	-
Asymptomatic hypercalcemia (%)	0	0	0	12%	-

* Related references

Table 4. Demographic, clinical, biochemical, radiological findings and parathyroid gland weights in Iranian patients with PHPT

Characteristic / Measurement	Iran (Tehran- Shiraz-Tabriz)
Time period	1978-2003
Total number	356
Gender ratio (F:M)	8:1
Age at presentation (mean \pm SD. Years)	39 \pm 14
Bone disease	60-100%
Osteitis fibrosa cystica	>50%
Palpable brown tumors	Frequent
Fractures	Frequent
Nephrolithiasis	14.5-47%
Nephrocalcinosis	<5%
Serum Calcium, mg/dL (mean \pm SD)	11.2 \pm 1.1
Alkaline phosphatase, IU/L (mean \pm SD)	657 \pm 116
PTH, pg/mL (mean \pm SD)	513 \pm 486
24-h Urinary Ca, mg/day (mean \pm SD)	224 \pm 129
Parathyroid gland weight g, mean (range)	4.1 (0.8-25)*

* Reported in 177 cases

Sex and age distribution

There were 317 females and 49 males with a female to male ratio of 6.4: 1, and an age range from 11 to 72 years, with a mean age of 38.2±12.4 years.

Clinical presentation

Most patients presented with an advanced form of skeletal involvement; bone pains, localized bone tumors, fractures and deformities were present in 60–100% of patients. Renal disease was a less frequent mode of presentation. Nephrolithiasis was diagnosed in 14–47% of patients.

Laboratory findings

Most patients had persistent hypercalcemia. Mean serum calcium concentration was 11.2±1.1 mg/dL. Serum calcium was normal in 4.6–16.5% of reported patients. The vast majority of patients had high serum PTH and low serum phosphorus levels.

Radiological findings

Nearly all patients displayed some radiological changes, suggestive of hyperparathyroid bone disease. Osteoporosis, subperiosteal bone resorption, salt and pepper appearance, brown tumor and pathologic fractures were frequent x-ray findings.

Pathological features

Single adenoma was discovered in most patients; four gland hyperplasia and double adenoma were less frequent pathological findings. There were four cases with parathyroid carcinoma. Mean parathyroid gland weight, reported in 177 cases, was 4.1 g, with a range of 0.8–25 grams.

Discussion

Primary hyperparathyroidism which is a relatively common endocrine dysfunction is characterized by unregulated PTH secretion and resulting hypercalcemia. Over the past half century, the pattern of clinical presentation of the disease has changed dramatically in developed countries. Indeed PHPT has evolved from a severe disease to an asymptomatic condition or disorder with more subtle manifestations.⁵⁻⁹ The story is completely different in hyperparathyroid patients from Iran and other eastern countries. Primary hyperparathyroidism still presents with the traditional pattern of bones and stones in developing countries. There are striking similarities between clinical and laboratory findings of PHPT from Iran and other eastern regions (Table 5), while major differences are evident between features of PHPT from these regions

Table 5. Results of studies in PHPT patients reported from developing countries

Parameter (%)	Study					
	Bahrami Iran(15)*	Atefi Iran(14)*	Gazi Iran(12)*	Bhansali North India(23)*	Harinarayan India(20)*	Cheung Hong Kong Chinese(17)*
Female to male ratio	5:1	9:1	5:1	3.3:1	2:1	1.5:1
Mean age of patients (y)	38.6	34	36.2	36:3	38	42
Most common form of presentation	skeletal	skeletal	skeletal	skeletal	skeletal	skeletal
Bone disease (%)	93.5	100	100	86.5	90	74
Renal disease (%)	14.5	22.5	47	70	50	39
Asymptomatic hypercalcemia	0	0	0	0	0	0

*Related references

and those of subjects from developed nations (Table 2); these differences are:

1) In the West, PHPT mainly affects middle aged females with a peak incidence between the fifth and sixth decades of life, with a female to male ratio, of 2–3:1.^{4,5,9} In developing countries, the peak incidence among both sexes is reported to be in the fourth decade of life, in other words, patients from these countries belong to younger age groups.¹⁸⁻²⁶ The reason why patients from developing nations present at a younger age is not clear; obviously delay in diagnosis is not a logical explanation. Coexisting vitamin D deficiency could be a factor.

2) The vast majority of patients from developing countries present with severe bone disease.¹⁸⁻²⁶ Bone involvement closely resembles that originally described by Albright and Reifenstein.^{1,2} Experiences from several developing countries including our own show a high percentage of advanced bone disease in patients with PHPT.^{18-26,51} Some investigators explained the high percentage of bone involvement with florid presentation by the common coexistence of vitamin D deficiency, prolonged PHPT, and low calcium intake.²¹

3) Renal disease is considerably less frequent in patients with PHPT from developing countries.¹⁸⁻²⁶ This is in sharp contrast to the results reported from western countries, where prior to the introduction of routine serum calcium measurement, renal disease was the most common clinical form of PHPT.³⁻⁵ The low frequency of renal involvement in patients from developing countries could be attributed to the absence of significant hypercalciuria, due to low mean serum calcium levels, most probably resulting from low dietary calcium consumption and or vitamin D deficiency; supporting this is the high prevalence of normocalcemic PHPT in many studies from developing countries, where its prevalence has been reported from range between 3 and 50%.¹³⁻²⁰ Normocalcemic PHPT with bone and/or stone disease is an excep-

tion rather than the rule in the West.^{27, 28} Could vitamin D deficiency be the main responsible factor for many of the major differences in presentation of PHPT between patients from developing nations and those from developed countries?

From the stand point of biochemical findings, hypercalcemia is the diagnostic hallmark of primary hyperparathyroidism and nearly all patients belonging to western countries have hypercalcemia.⁹ Although it has been reported that patients may present with serum calcium levels within normal ranges but normocalcemic hyperparathyroidism in subjects with bone and/or kidney involvement is a rare finding in the West, in contrast to the prevalence of normocalcemic hyperparathyroidism, reported to range from 3–50% in developing countries.^{19–27}

Results of some investigations have shown that vitamin D status might influence the clinical and biochemical features of PHPT.²⁸⁻³¹ Low serum vitamin D levels in patients with PHPT were associated with worsening laboratory, densitometric and histomorphometric indices of bone involvement and a high risk of fractures.^{32,33} Likewise, results of many studies have shown that coexisting vitamin D deficiency might result in advanced osteitis fibrosa cystica.³⁴⁻³⁷ Others have reported that parathyroid gland weight was greater in patients with PHPT, who had coexisting vitamin D deficiency and severe bone disease.^{29, 31-33} On the other hand, supplementation with calcium and vitamin D was associated with a significant increase in bone mineral density in PHPT patients with coexisting vitamin D deficiency.³⁹ Such observations have led an expert panel to offer vitamin D supplements to asymptomatic PHPT patients with coexisting vitamin D deficiency.³⁹

The studies carried out in the two preceding decades have shown a high prevalence of vitamin D deficiency, ranging between 30-93%, in developing countries including China, Turkey, India, Iran and Saudi Arabia.⁴³⁻⁴⁹ Recent stud-

ies performed in our country showed high prevalence of vitamin D deficiency in adult urban populations of both sexes.^{49,50} Although vitamin D status was not reported in many of studies performed in PHPT patients, but due to a widely prevalent vitamin D deficiency in developing countries.⁴³⁻⁵⁰ such highly prevalent and advanced bone disease in hyperparathyroid patients can be attributed to a coexisting vitamin D deficiency. Obviously vitamin D deficiency is not the only factor in determining the severity of bone involvement in hyperparathyroid patients from developing nations and other, yet unknown, pathogenetic factors may play contributory role.

In conclusion, PHPT is a severe, symptomatic disease with serious complications and high morbidity in developing countries. Advanced skeletal disease is the most common pattern of presentation at a young age. Vitamin D deficiency might influence the clinical and biochemical expression of PHPT. Routine measurement of serum calcium concentration, at least in high risk subjects (middle-aged females), awareness of protean manifestations of the disease and vitamin D supplementation will facilitate early diagnosis and prevention of its major complications and associated morbidities

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