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ORIGINAL ARTICLE

Advanced Bone Disease as the Most Common Clinical Presentation of Primary Hyperparathyroidism In Iranians: Clinical And Laboratory Features of 62 Patients from North-Western Iran

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The original studies of Albright and Reifenstein characterized primary hyperparathyroidism as a disease of "bones and stones". The disease at present is recognized most frequently as a totally asymptomatic condition, detection being based on the finding of hypercalcemia in the routine screening of serum calcium levels. The purpose of this cross sectional clinical case study was to analyze the clinical, biochemical, radiological, and pathological features of the disease in Iranians and to compare these features with those of patients from western countries.

Materials and Methods: From 1985 through 2002, sixty-two patients with primary hyperparathyroidism were studied from the north-western part of Iran. In addition to routine studies, the following evaluations were conducted; 1) measurements of serum calcium, phosphorous, alkaline phosphatase, creatinine and electrolytes; 2) X-rays of skull, hands, clavicles, pelvis, vertebral bones, abdomen, long bones, and dental film of lamina dura, and 3) Intravenous pyelogram and/or ultrasonography of kidneys. PTH was measured in only 29 patients because of lack of reliable laboratory methods during the earlier years of the study. Surgery was performed in all subjects and they were followed postoperatively.

Results: There were 52 females and 10 males, with a female to male ratio of 5.2:1, and an age range of 13 to 71 years with a mean age of 38/6 years. The peak incidence in both sexes was in the 4th decade. The vast majority of patients in this series presented with symptoms referable to skeletal involvement. Fifty-eight (93.5%) patients suffered from bone pains, deformities, pathologic fractures, and localized bone tumors. Renal colic was a less frequent complaint; only in 4 patients (6.4%) clinical renal disease led to the diagnosis of hyperparathyroidism. No patient was asymptomatic. Fifty-four patients had persistent hypercalcemia. In 3 patients hypercalcemia was intermittent and 5 patients were normocalcemic. Mean serum calcium concentration was 11.2 mg/dl (range 9.3-15.6 mg/dl). A high proportion of the patients, 49 of 62, had low serum phosphorus level. Mean serum phosphate concentration was 2.1 mg/dl (range 1.4-3.6 mg/dl). Interestingly, all 5 normocalcemic patients were hypophosphatemic. Serum alkaline phosphatase level was elevated in 56 patients, and PTH concentration was high in all the 29 patients in whom it was measured. All patients displayed some radiologic changes. Subperiosteal resorption of phalanges and/or distal clavicles was the most frequent (43/62) radiologic finding. Salt and pepper appearance on skull x- rays, brown tumor

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in pelvis, metacarpals, and long bones were other common radiologic features. Pathologic fractures were found in 32 patients, including vertebral collapse in 3 patients. The pathologic findings were single adenoma in 54 patients, double adenoma in 3 subjects, hyperplasia in 4 patients (2 patients with MEN –1 and one with MEN-2), and parathyroid carcinoma in 1 patient.
Conclusion: This study shows that advanced bone disease is the most frequent clinical presentation of hyperparathyroidism in Iranians. Routine serum calcium measurement is recommended at least in high-risk patients, in particular for females in their 4th – 5th decades of life.

Key Words: Hyperparathyroidism, Iranians, Clinical **presentation**

Introduction

Primary hyperparathyroidism is characterized by hypercalcemia in association with elevated serum levels of parathyroid hormone (PTH). The original studies of Albright and Reifenstein characterized primary hyperparathyroidism as a disease of "bones and stones".[1-3] In some patients, the disease was complicated by renal involvement. Renal diseases, particularly recurrent nephrolithiasis were present in nearly 60% of patients. In others, a distinctive bone disease predominated. Osteitis fibrosa cystica was the hallmark of classic primary hyperparathyroidism. Bone pain, fractures and skeletal deformities were not uncommon. Brown tumor of the long bones, subperiosteal bone resorption, "salt and pepper" - appearing erosions of the skull, and pathologic fractures were common radiographic findings.[1-4] With the advent of the automated serum chemistry autoanalyzer in the 1970s, the diagnosis of primary hyperparathyroidism became much more common, with a four- to fivefold increase in its incidence, but classic manifestations of the disease became much less common. The disease at present is recognized most frequently as a totally asymptomatic condition, detection being based on the finding of hypercalcemia in the routine screening of serum calcium levels.[5-9] In the United States, complicated primary hyperparathyroidism is now the exception rather than the rule. In fact, more than 80% of patients having no symptoms or signs attributable to their disease.[9] Recent studies have shown that the incidence of renal disease has been reduced from 30 to 50%, common in the past, to 10-15% of patients currently.[10] There is clearly also a changing pattern of skeletal manifestations of hyperparathyroidism. Osteitis fibrosa cystica, the classic form of skeletal disease in hyperparathyroidism is declining sharply in relative frequency. In an analysis of 138 cases, it was noted that, during the decades between 1930 and 1949, fifty-three percent of patients had symptomatic osteitis fibrosa cystica, but no skeletal symptoms at all were detected in the 58 patients with primary hyperparathyroidism seen between 1980 and 1983. In other words hyperparathyroidism has, in the western world, evolved from its classical presentation in the past to an asymptomatic disease at present. This cross-sectional clinical case study concerns 62 patients with primary hyperparathyroidism. The purpose of the study was to analyze the clinical, biochemical, radiological, and pathological features of the disease in Iranians and to compare these features with those of patients from western countries.

Materials and Methods

This study was conducted at Tabriz University of Medical Sciences, in north- western Iran. During a 17-year period, between 1985 and 2002, a total of 62 patients with primary hyperparathyroidism were studied at endocrine clinics.

In addition to routine studies, the following evaluations were conducted in all patients: 1) serial measurements (at least twice and preferably 3-times, on separate days) of serum calcium, phosphorus, alkaline phosphatase, creatinine, and electrolytes by routine laboratory methods, with at least one determination in a reliable referral laboratory; 2) radiologic investigations including x-rays of skull, hands, clavicles, pelvis, long bones, spines and dental films of lamina dura; 3) KUB, in-

travenous pyelogram and/or ultrasonography of kidneys. Serum PTH was measured by the IRMA technique in only 29 subjects because of lack of reliable laboratory methods duting first seven years of the study. Urinary calcium excretion was determined in 34 patients. The diagnosis of primary hyperparathyroidism was made using two or more of the following criteria: a) elevated serum calcium in the presence of normal or high serum PTH levels; b) hypercalcemia along with radiologic skeletal findings characteristic of hyperparathyroidism; c) high serum calcium in patients in whom other causes of hypercalcemia were excluded; and d) histologic proof of parathyroid adenoma or hyperplasia (after parathyroidectomy). Surgery was performed in all patients and they were followed postoperatively.

Results

Sex and age distribution: There were 52 females and 10 males among this series with a female to male ratio of 5.2:1. The age of patients ranged from 13 to 71 years with a mean age of 38.6±11.5 years. The peak incidence among both sexes was in the fourth decade of life. Twenty-nine subjects (47%) belonged to the age group of 31-40 years.

Clinical features: The vast majority of patients presented with symptoms referable to skeletal involvement. Fifty-eight patients (93.5%) suffered from bone pains, localized bone tumors, fractures, and deformities. Other common symptoms in decreasing order of frequency were fatigue, weakness, arthralgia, gastrointestinal complaints and muscle weakness (Table 1). Renal colic was a less frequent compliant, only in 4 patients (6.5%) clinical renal disease led to the diagnosis of hyperparathyroidism. No patient was asymptomatic at the time of diagnosis.

Laboratory findings: Fifty-four patients (87%) had persistent hypercalcemia. In 3 subjects hypercalcemia was intermittent. Five patients (8%) had normal serum calcium on serial measurements. Mean serum calcium concentraction was 11.2 mg/dL (range 9.3 – 15.6 mg/dL). A high proportion of patients (79%) had hypophosphatemia. Mean serum phosphorus level was 2.1 mg/dL. Interestingly, all 5 normocalcemic subjects had low

Table 1. Frequency of clinical symptoms of primary hyperparathyroidism in 62 subjects

Manifestation	Patients (No.)	Frequency (%)
Skeletal symptoms (pain, fracture, tumor, and deformity)	58	93
Fatigue and weakness	54	87
Arthralgia	48	77
Gastrointestinal complaints	39	63
Polyuria	28	45
Muscle weakness	21	34
Weight loss	21	34
Slow mentation	16	26
Depression	14	22
Hypertension	13	21
Renal colic	4	6
Generalized pruritus	2	3
Acute pancreatitis	1	1
No symptoms	0	0

serum phosphorus concentrations. Serum alkaline phosphatase level was elevated in 56 (90%) patients. Serum concentration of alkaline phosphatase was directly related to extent of bone disease and presence of pathological fractures. Serum PTH level was high in all the 29 patients in whom it was measured; its mean concentration was 184±41 pg/mL. (Table 2). The mean 24-hour urinary calcium excretion rate measured in 34 patients was 162±23 mg/day; only in 3 subjects, this level was higher than 200 mg/day.

Radiologic findings: All patients displayed some radiographic changes suggestive of hyperparathyroid bone disease in different combinations. Osteopenia was the most consistent radiologic finding reported. Subperiosteal resorption of phalanges and / or distal clavicles was evident in 48 patients (77.5%). Salt and pepper appearance on skull x-rays, brown tumors in pelvis, long bones, and metacarpals were other common radiologic features. Epulis, a giant cell tumor of the mandible or maxilla was the presenting complaint in 4 patients (Table 3). Pathologic fractures were evident in 32 patients radiologically. Common sites of fracture were pelvic and long bones. Three patients had vertebral collapse. In some patients there was more than one site of fracture (Table 4). Renal disease was present in 9 patients (14.5%). The patterns of kidney involvement were nephrolithiasis in 7 cases and nephrocalcinosis in 2 others (Fig.1).

Pathologic findings: These were single adenoma in 54 cases (87%), double adenoma in 3 patients, four gland hyperplasia in 4 patients (2 subjects with MEN– 1 and one with MEN-2), and parathyroid carcinoma in one patient. The majority of adenomas were more than 1 cm in diameter with mean diameter size of 2.2 cm. In one patient with parathyroid carcinoma the tumor was 4 cm in diameter and serum PTH was reported to be 1300 pg/mL.

Table 2. Biochemical profile in 62 individuals with primary hyperparathyroidism

	Biochemical concentration		
	Mean ± SD	**Range**	**% of patients with abnormal result**
Serum calcium (mg/dL)	11.2 ± 1.1	9.3 – 15.6	92
Serum phosphorus (mg/dL)	2.1 ± 0.2	1.4 – 3.6	79
Serum alkaline phosphatase (IU/L)	657 ± 116	84 ± 3150	90
Serum PTH * (pg/mL)	184 ± 41	76 – 1300	100
24 hour urinary calcium excretion**	162 ± 23	58 – 291	0

* PTH was measured in 29 subjects

** 24 hour urinary calcium was determined in 34 patients

Table 3. Frequency of radiologic findings in 62 patients with primary hyperparathyroidism

Abnormal radiologic finding	**No. of patients**	**Frequency (%)**
Subperiosteal bone resorption	48	77
Salt and pepper appearance of skull	39	63
Brown tumor including jaw tumors (epulis)	37	60
Pathologic fractures	32	51
Loss of lamina dura of the teeth	25	40
Nephrolithiasis	7	11
Nephrocalcinosis	2	3
Chondrocalcinosis	1	1

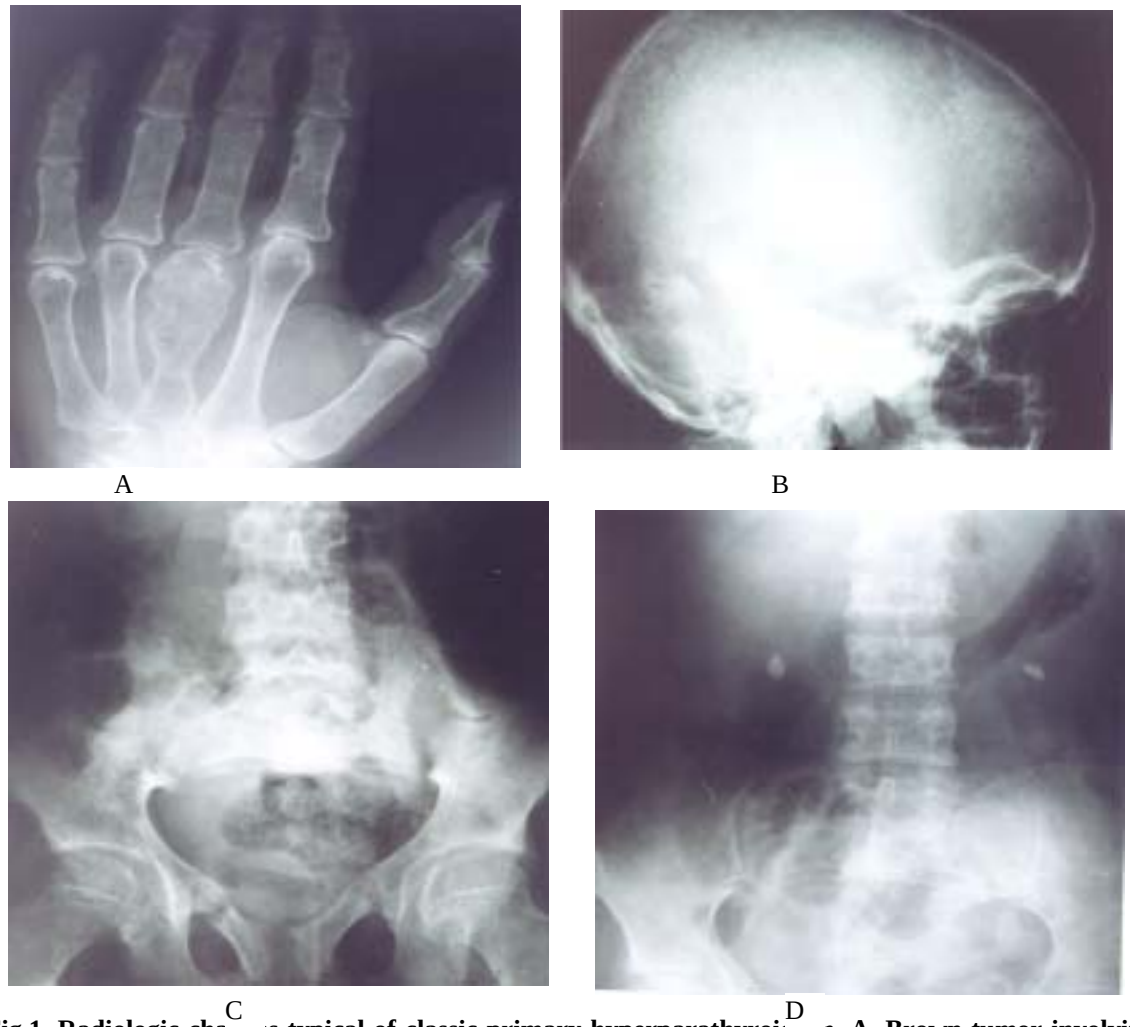

Fig.1. Radiologic changes typical of classic primary hyperparathyroidism. A. Brown tumor involving third metacarpal bone. B. Typical salt and pepper appearance. C. Pelvic fractures. D. Bilateral renal stones

Tatble 4. Frequency and sites of pathological fracures in 62 patients with primary hyperparathyroidism

Fracture site	Frequency* (%)
Femoral and pelvic bones	18 (29)
Tibia and fibula	8 (13)
Long bones of arms and forearms	9 (14.5)
Metatarsal bones	4 (6.5)
Metacarpal bones	3 (5)
Vertebral bones	3 (5)
Ribs and scapula	2 (3)

* In some patients there was more than one site of fracture

Discussion

Primary hyperparathyroidism is a disorder characterized by excessive parathyroid hormone (PTH) production and resulting hypercalcemia. The major physiologic actions of PTH, when driven to excess, lead to the potential for major complications at the level of bones and kidneys.[1-4]

The original studies of Albright and Reifenstein characterized primary hyperparathyroidism as a disease of "bones and stones" Osteitis fibrosa cystica was the hallmark of classic primary hyperparathyroidism and re-

nal involvement manifested by nephrolithiasis or nephrocalcinosis was present in nearly 80% of patients.[1-4] The disease today bears little resemblance to the severe disorder of "bones and stones" with accompanying severe morbidity and mortality in Western countries. Indeed primary hyperparathyroidism has evolved over the last three decades from a disease with dramatic presentation to a disorder with more subtle manifestations (Table 5).[9] The reason for this dramatic change in disease manifestations is almost certainly the improved diagnostic approaches. With the advent of the automated chemistry analyzers with routine determination of serum calcium, the diagnosis of primary hyperparathyroidism has become much more common, with a five – fold increase in its incidence, whereas the classic presentation of the disease, has become much less common.[5-9] In Western countries symptomatic primary hyperparathyroidism is now the exception rather than the rule with more than 80% of patients having no signs or symptoms referable to their disease.[6,7,11] Recent studies have shown that the incidence of renal disease has been reduced from 30 to 50% common in the past to 10-15% of patients currently.[9-10] There is clearly also a changing pattern of skeletal manifestations of hyperparathyroidism. Osteitis fibrosa cystica, the classic form of skeletal disease in hyperparathyroidism is declining sharply in relative frequency.[5-7,11]

Table 5. Changing profile of primary hyperparathyroidism

	Study			
Symptomatology	**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

Table 6. Results of this study in comparison with results reported from western countries

Parameter	**Present study**	**Western countries**	
		Before 1970s	**After 1970s**
Female to male ratio	5:1	2:1	3 – 4: 1
Mean age of patients (year)	38.6	52.4	53.7
Most common pattern of presentation	Bone disease	Renal disease	Asymptomatic hypercalcemia
Bone disease (%)	93.5%	%15 – 20	Rare
Renal disease (%)	14.5%	%50 – 70	%7 – 10
Asymptomatic hypercalcemia (%)	0	%3 - 5	%50 - 60

Table 7. Results of this study in comparison with results reported from other developing countries

Parameter	Present study	Bhansali India (18)*	Gazi Iran (49)*	Atefi Iran (17)*	Harinarayan India (15)*	Cheung Hong Kong (12)*
Female to male ratio	5:1	3.3:1	5:1	9:1	2:1	1.5:1
Mean age of patients	38.6	36:3	36.2	34	38	42
Most common form of presentation	skeletal	skeletal	skeletal	skeletal	skeletal	skeletal
Bone disease (%)	93.5%	86.5%	100%	100%	90%	74%
Renal disease (%)	14.5%	70%	47%	22.5%	50%	39%
Asymptomatic hypercalcemia (%)	0	0	0	0	0	0

* Related references

In an analysis of 138 cases, it was noted that, during the decades between 1930 and 1949, fifty-three percent of patients had symptomatic osteitis fibrosa cystica,[46] but no skeletal symptoms whatsoever were detected in the 58 patients with primary hyperparathyroidism seen between 1980-1983.[47] Among the first 343 cases reported in 1966 from the Massachusetts General Hospital, 57% of patients had nephrolithiasis, 23% had skeletal involvement and less than 1% were asymptomatic.[3]

The story is completely different in Iranian patients with primary hyperparathyroidism. There are clearly major differences between features of hyperparathyroidism in our patients and those of peoples reported from developed nations (Table 6); these differences are:

One: In developed countries, hyperparathyroidism mainly affects middle aged patients with a peak incidence in the sixth to seventh decades of life and a female to male ratio of 2-3:1.[4,5,9,45] In our series, the peak incidence among both sexes was in the fourth decade of life and approximately half of the patients belonged to the age group of 31-40 years. The female to male ratio was 5.2:1. In other words, our patients belonged to younger age groups and most of them were females. These finding are in agreement with reports from other developing countries.[12-16] In the Indian experience, mean age of patients was 38±15 years.[14-16] Atefi S. reported on 40 patients with primary hyperparathyroidism from Shiraz, south of Iran; there were 36 females and 4 males, with a mean±SD age of 34±12 years.[17] In an interesting study conducted by Mir Saeid Gazi and co-workers on 30 cases of primary hyperparathyroidism from Tehran, Iran, there were 25 females and 5 males with a mean age of 36.2±10 years.[49] The reason why Iranian hyperparathyroid patients present at a younger age is not clear. Obviously, delay in diagnosis is not a logical explanation. Coexisting vitamin D deficiency as described in a few previous studies from developing nations could be a factor, but this was not a consistent finding.

Two: The vast majority of patients in this study presented with skeletal symptoms. Fifty-eight patients (93.5%) suffered from bone aches and pains, localized bone tumors, fractures, and deformities. Radiologic investigations confirmed the presence of hyperparathyroid bone disease on plain x - rays in nearly all patients (Table 3), and alkaline phosphatase, as a marker of bone involvement, was significantly elevated in 90% of cases (Table 2).

Bone involvement in Iranian hyperparathyroid patients (Tables 3 and 4) closely resembles that classically described by Albright and Reifenstein about 60 years ago. The situation in our country is also very similar to experiences from other developing countries,[12-16,18] which showed a high percentage of osteitis fibrosa cystica in hyperparathyroid patients (Table 7). In an excellent study by Mir Saeid Gazi et al. skeletal involvement was the most common pattern of presentation of primary hyperparathyroidism. Almost all patients in their series presented with bone pain and had radiologic evidences of bone disease. Forty-seven percent suffered from bony fractures.[49] Atefi S. reported his experience with 40 patients with primary hyperparathyroidism from Shiraz, south part of Iran;[17] in his series, 80% of patients suffered from bone aches and pains and 7.5% had pathologic fractures. In a recent description of 52 hyperparathyroid patients from north India, bone disease was the commonest mode of presentation. In a study done in India, Harinarayan et al reported clinical, radiological, biochemical and histopathologic features of 20 consecutive cases of primary hyperparathyroidism.[15] Ninety percent of patients presented with a history of bone pains, and 40% with bone fractures. A radiological picture of osteitis fibrosa cystica was found in the vast majority. Plasma 25-OHD_3 levels were assessed in all 20 patients and 14 healthy age and sex matched controls. The mean value of 25-OHD3 was 8.4±5.1 μg/L for patients and 8.2±2.5 μg/L for control group, seven out of 20 showing 25-OHD3 below 5 μg/L; they explained the high percentage of skeletal involvement of 95% with florid presentation by the common coexistence of vitamin D deficiency and concluded that the predominant bone disease was probably due to prolonged primary hyperparathyroidism coexisting with low calcium intake and / or 25-OHD3 deficiency.[15] The effect of vitamin D deficiency on the severity of bone disease of primary hyperparathyroidism was investigated by H. Raef et al in a vitamin D deficient region of Saudi Arabia.[50] They concluded that vitamin D deficiency is a contributing factor to severity of bone disease. Some investigators have shown that coexisting vitamin D deficiency may result in an advanced osteitis fibrosa cystica.[19,20,33-36,41,42] Others have reported that parathyroid gland weight was greater in patients with hyperparathyroidism who had vitamin D deficiency and severe bone disease.[36-40]

The studies carried out in the preceding two decades have shown a high prevalence of vitamin D deficiency in tropical countries,[22-30] which varied between 30% and 93%. Recent studies performed in our country showed high prevalence of vitamin D deficiency in adult urban populations of both sexes.[31-32]

Plasma 25–hydroxyvitamin D concentrations were not measured in our hyperparathyroid patients, but due to widely prevalent vitamin D deficiency in our country,[31-32] such highly prevalent and advanced bone disease can be attributed to a coexisting vitamin D deficiency. Obviously this is not the only factor in determining the severity of bone involvement in Iranian hyperparathyroid patients and other unknown pathogenetic factors may exist.

Three: Prior to the introduction of routine serum calcium measurement using the autoanalyzer, renal disease was the most common clinical from of primary hyperparathyroidism in Western countries.[3-5] Renal disease, particularly recurrent nephrolithiasis was present in nearly 60% of patients (Table 6). Recent reports from the West have shown that the incidence of hyperparathyroid renal disease has fallen to less than 5 to 10% (Table 5). This is probably due the earlier diagnosis of the disease today at the, asymptomatic phase.[5,6,9,10] In the present study, renal colic was a less frequent complaint, and only in 4 patients (6.4%) clinical renal disease led to the diagnosis. At the end of work ups, renal involvement was confirmed in 9 subjects (14.5%); nephrolithiasis was shown in 7 cases and nephrocalcinosis in two others. This confirms that renal disease is considera-

bly less frequent in our hyperparathyroid patients. The situation is in sharp contrast to the results obtained from previous investigations, not only those from the West but also of developing countries.[13-16,18] In the Harinarayan, and co - workers' study, renal stones and/or nephrocalcinosis was present in 50% of patients.[15] Many of the patients in their series were vitamin D deficient, 50% were normocalcemic, but 90% had hypercalciuria as shown by 24 – hour urinary calcium excretion or Ca/Cr ratio. In studies, both from developed and developing countries, a significant proportion of hyperparathyroid patients had hypercalciuria but there was not a direct positive correlation between hypercalciuria and incidence of renal stone formation.[3-16] In an interesting study performed by SJ.Silverberg et al to compare hyperparathyroid patients with and without nephrolithiasis with regard to biochemical profile and presence and extent of bone involvement, total daily urinary calcium excretion was higher in stone formers.[10] The mean daily urinary calcium excretion measured in 34 patients in our series was 162 ± 23 mg, the amount being well below than that reported in other studies. The absence of hypercalciuria in the majority of our patients resulting from low mean serum calcium levels (11.2± 1.1 mg/dL), most probably due to low dietary calcium consumption and/or vitamin D deficiency, may be one of the underlying mechanistic factors responsible for low frequency of nephrolithiasis.

Four: Hypercalcemia is the diagnostic hallmark of primary hyperparathyroidism and the vast majority of patients from Western countries have hypercalcemia.[9] It has been accepted that patients with primary hyperparathyroidism, may present with serum calcium levels that are within normal range. Normocalcemic hyperparathyroidism with bone and/or stone disease is an exception rather than rule in the West.[35,36] In our series, five patients (8%) had normal serum calcium concentrations on serial measurements. Interestingly, all 5 normocalcemic subjects had low serum phosphorus levels and high alkaline phosphatase activity. This finding is in agreement with results of many studies from developing countries, where the prevalence of normocalcemic hyperparathyroidism has been reported from 3 – 50%.[13-18] Could vitamin D deficiency be the main responsible factor for many of the major differences in presentation of primary hyperparathyroidism between peoples from developing nations and those from developed countries? Silverberg et al. studied the effects of vitamin D insufficiency in patients with primary hyperparathyroidism and found that patients with the lowest serum levels of 25OH D3 had significantly greater serum PTH concentrations and serum alkaline phosphatase activity. Serum phosphorus levels were lower than those in patients with higher 25OH D3 levels.[42] However, the biochemical, densitometric and histomorphometeric indices of bone involvement were far milder than those in our series. Mishra et al in their study of clinical characteristics of primary hyperparathyroidism in India, showed severe variant of the disorder in vitamin D-sufficient Indians and concluded that factors other than vitamin D deficiency may play a role in the development of primary hyperparathyroidism in Indians and other developing nations.[16]

In conclusion, primary hyperparathyroidism is a severe, symptomatic disease with serious complications in Iranians. Advanced skeletal disease is the most common pattern of presentation at a young age. Routine serum calcium measurement and awareness of the protean manifestations of the disease will facilitate early diagnosis and prevention of its major complications and associated morbidities.

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