

PRIMARY HYPERPARATHYROIDISM: KING KHALID UNIVERSITY HOSPITAL EXPERIENCE

Mona A. Fouda, MBBS, MRCP

Background: This study was conducted to examine the prevalence, mode of presentation and management of primary hyperparathyroidism in one of the major hospitals in Saudi Arabia.

Patients and Methods: This was a retrospective analysis of 24 cases of primary hyperparathyroidism, comprising 21 females and three males, who were seen at King Khalid University Hospital over a period of 16 years from 1982 until December 1997.

Results: The prevalence of the disease was estimated to be 11.34 per 100,000 hospital population. The majority of the patients presented with musculoskeletal complaints (62%-67%) and/or renal complications (58%). Hypercalcemia was seen in 92% of the cases. Serum PTH was available for 21 patients and 20 had significantly elevated levels. Fifty percent of the patients had features of hyperparathyroid bone disease on plain x-ray, while 79% showed osteopenia of the femoral neck on dual x-ray absorptiometry, and almost all the patients had lumbar osteopenia. Fifty percent of the patients had features of metabolic bone disease on bone scan. Thallium-technetium subtraction studies proved to be the most reliable tool, with 83% sensitivity, followed by ultrasound scan of the neck, with a sensitivity of 55%. CT scan of the neck was attempted in only seven patients (29%), with a sensitivity of 86%. Twenty-one patients (87.5%) underwent surgical exploration and removal of the parathyroid adenoma. Single parathyroid adenoma was identified in 85% of the cases, 5% had multiple adenomas, and 5% had hyperplasia of the parathyroid gland.

Conclusion: Our results showed that primary hyperparathyroidism is not a rare disease in Saudi Arabia. It has a tendency for late presentation with complications. We believe that routine screening for calcium and early identification of such cases are warranted to reduce the morbidity of this easily treatable disorder.

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Primary hyperparathyroidism is a relatively common disorder in Western countries, with an annual incidence of 28 per 100,000 population in the USA.¹ The disease has evolved over the last three decades from a multisystem disorder, often with complications, to a commonly asymptomatic disease picked up by routine serum calcium analysis. This has been the usual experience in Western countries, but in Asia, especially the Indian subcontinent,² the clinical presentation of the disease continues to be the same as that described by Albright et al.,³ and Albright and Reifenstein⁴ in the early half of this century.

In Saudi Arabia, we are aware of only one published report on the presentation of hyperparathyroidism in the Eastern province.⁵ Primary hyperparathyroidism is not a commonly encountered disease in the Kingdom, even in areas where screening for serum calcium is not routinely

done, but severe complicated cases of skeletal and/or renal manifestation of the disease are still seen. This paper attempts to evaluate the prevalence and clinical presentation of primary hyperparathyroidism, as seen in one of the major teaching hospitals in Saudi Arabia.

Patients and Methods

The present study was conducted at King Khalid University Hospital (KKUH), a 750-bed tertiary healthcare center and teaching institution with over 300,000 outpatients and over 24,000 admissions per year. KKUH is one of the seven major healthcare centers in Riyadh, which serve a community of about 2.6 million residents. KKUH maintains a well-organized and centrally computerized system of patients' medical records.

Twenty-nine potential cases of primary hyperparathyroidism were identified from the central diagnostic index database from 1982 until 1997. Of the 29 patients, five did not have enough clinical or biochemical evidence to support the diagnosis and were therefore excluded from the study. The medical records of the remaining 24 patients were retrospectively reviewed for age, sex, marital

From the Department of Medicine, King Khalid University Hospital, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Fouda: Department of Medicine, King Khalid University Hospital, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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status, growth parameters, previous medical history, presenting signs and symptoms, routine biochemical investigations, radiological and surgical procedures, and histological findings. The diagnosis of primary hyperparathyroidism was based on one or more of the following criteria: 1) histopathological evidence (after parathyroidectomy) of parathyroid adenoma and/or hyperplasia; 2) persistent elevation of serum calcium above 2.60 mmol/L, excluding any other demonstrable cause of hypercalcemia; and 3) increased circulatory immunoreactive parathyroid hormone (PTH), along with pathognomonic radiographic features.

The serum chemistry and 24-hour urine for calcium and phosphorus were determined by multichannel autoanalyzers in the central Hospital laboratory, with the normal ranges being 2.12-2.60 mmol/L for serum calcium (Ca), 0.80-1.40 mmol/L for serum phosphorus, 43.0-154 U/I for serum total alkaline phosphatase (SAP), 2.5-7.5 mmol/day for urinary calcium, and 13-42 mmol/day for urinary phosphorus. The serum parathyroid hormone (PTH) radioimmunoassay was performed at Biocentia Laboratories, Germany, with the normal range being 5-50 pmoles/L.

Radiological investigations included skeletal survey, parathyroid scan (thallium-technetium subtraction study), ultrasound and CT scan of the neck, bone mineral densities (BMD) of femoral neck and lumbar spine (L₂-L₄) by dual x-ray absorptiometry (DXA), as well as Tc-99m bone scan. Normal BMD ranges were 1.143±0.105 g/cm² for the lumbar spine and 0.959±0.100 g/cm² for the femoral neck for Saudi women (age 20-40 years; peak bone mass),⁶ and 1.142±0.096 g/cm² for the lumbar spine and 1.036±0.133 g/cm² for the femoral neck for Saudi men (age 20-40 years; peak bone mass).⁶

Parathyroidectomy was performed under general anesthesia. Depending upon the radiological findings, the four parathyroid glands were evaluated grossly before determining the extent of resection. If a single gland disease was present, the enlarged gland was removed and sent for histopathological studies. If more than one gland was involved, then all the diseased glands were resected and sent for histopathological analysis.

The data was analyzed, using StatPack Gold[®] statistical analysis package. Data were summarized as mean±SD or proportions. A *P*<0.05 was considered to be significant.

Results

From 1982 to 1997, of the 211,706 patients admitted to KKUH, 24 were diagnosed as cases of primary hyperparathyroidism, a prevalence of 11.34 per 100,000 hospital admissions. Table 1 shows the patients' characteristics. There were 21 (87.5%) females and three (12.5%) males, with a mean±SD age of 44.0±13 (range, 14-65) years, with 14 (58%) of them above 40 (44-65) years of age. The

remaining 10 (42%) were below 40 (14-37) years. The mean age of the female patients (46±11.0, range 30-65 years) was significantly higher (*P*-value, <0.005) than males (28.0±10.0, range 14-36 years). The body mass index (BMI) of female patients was slightly higher than males, but was not statistically significant (*P*-value, 0.22).

Table 2 shows the clinical presentation of the patients. The most common and prominent manifestations of primary hyperparathyroidism involved the skeletal and urinary systems. The majority of our patients presented with bone aches (62.5%), generalized and proximal weakness (67%), single and multiple joints pain (67%), and recurrent renal calculi (58%). Some of the patients also reported lethargy and/or easy fatigability. Weight loss was seen in four patients. Abdominal complaints included constipation, pain, and vomiting. Other signs of hypercalcemia included polyuria, polydipsia and peripheral numbness and tingling. Three patients (12.5%) had diabetes mellitus and were on oral hypoglycemic agents. Hypertension as defined by a blood pressure of 150/100 mm Hg or greater was seen in four patients (17%) who had previous history of hypertension and use of antihypertensive drugs.

Table 3 shows the biochemical profile of the patients. Elevated serum calcium (>2.60 mmol/L) was detected in 22 out of 24 primary hyperparathyroid patients (92%), showing a mean concentration of 3.1±0.36 mmol/L (range, 2.7-3.86 mmol/L), with seven patients (32%) having a mean serum calcium of 3.56±0.29 mmol/L (range 3.22-3.86 mmol/L). Only two patients (8%) were normocalcemic, with a mean concentration of 2.48 mmol/L. Of the 22 hypercalcemic patients, men had a slightly higher but more statistically insignificant serum calcium level than women. Twenty-four-hour urinary calcium was reported in 18 (75%) patients. Of these, 13 (72%) had urinary calcium of 4.96±1.23 (range 2.4-6.5) mmol/day, which is within the normal range (2.5-7.5 mmol/day), while the remaining five (28%) showed elevated urinary calcium of 15.42±6.74 (range 7.6-25 mmol/day). However, the mean urinary calcium of all 18 patients was slightly above the normal range at 7.9±5.1 (range 2.4-25.0) mmol/day, thereby showing an overall mild hypercalciuria.

Serum phosphorus was reported in 23 patients (96%), with a mean value of 0.71±0.14 (range, 0.5-1.01) mmol/L,

TABLE 1. Demographics of 24 primary hyperparathyroid patients.

Variables	Male	Female	Total of cases
Sex	3 (12.5%)	21 (87.5%)	24
Age (years)	28.0±10.0 (14-36)	46.0±11.0 (30-65)	44.0±13.0 (14-65)
Nationality			
Saudi	2 (12.5%)	14 (87.5%)	16 (67%)
Non-Saudi	1 (12.5%)	7 (87.5%)	8 (33%)
BMI	23.56±11.0 (14-32)	28.0±6.5 (19-44)	27.0±7.0 (14-44)

TABLE 2. Clinical presentation of patients with primary hyperparathyroidism.

Signs/symptoms	Number (%)
Bone aches	15 (62.5)
Generalized/proximal weakness	16 (67)
Joint pains	16 (67)
Recurrent renal calculi	14 (58)
Lethargy/fatigue	3 (12.5)
Polyuria	7 (29)
Polydipsia	6 (25)
Hypertension	4 (17)
Weight loss	4 (17)
Constipation	4 (17)
Abdominal pain	4 (17)
Vomiting	2 (8)
Numbness and tingling	1 (4)

TABLE 3. Biochemical profile of patients with primary hyperparathyroidism.

Variable	Reference range ^a	N (24)	Concentration (mean±SD range)		
			Male	Female	Total
Serum calcium	2.12-2.60 mmol/L	24	3.5±0.51 (3.01-3.86) n=3	3.01±0.34 (2.36-3.86) n=21	3.05±0.39 (2.36-3.86)
Urinary calcium	2.5-7.5 mmol/day	18	16.62±9.5 (6.4-25.0) n=3	6.08-3.19 (2.4-15) n=15	7.9±5.1 (2.4-25.0)
Serum phosphorus	0.80-1.40 mmol/L	23	0.72±0.1 (0.66-0.83) n=3	0.71-0.16 (0.5-1.01) n=20	0.71±0.14 (0.5-1.01)
Urinary phosphorus	13-42 mmol/day	16	21.7±14.3 (11.6-31.83) n=3	11.02±7.8 (0.44-24.4) n=13	12.14±8.7 (0.44-31.83)
SAP	43-154 U/L	24	313.7±37.2 (273-346) n=3	544.0** (97-2828) n=21	297.50† (97-2828)
Serum PTH	5.0-55 pmol/L	21	444.3±270 (148-678) n=3	281±241.4 (50-870) n=18	304.05±245.53 (50-870)

^aAs per King Khalid University Hospital Central Laboratory standards; SAP=serum alkaline phosphate; PTH=parathormone **median value; n=number of patients who had the test done.

showing a mild overall hypophosphatemia (normal range 0.80-1.40 mmol/L). Of the 23 patients, 17 (74%) had serum phosphorus concentration below the normal range (0.64±0.08, range 0.5-0.77 mmol/L), while the remaining six patients (26%) were normophosphotemic, with a mean level of 0.92±0.1 (range, 0.83-1.01) mmol/L. Twenty-four-hour urinary phosphorus was done in 16 patients (67%), who had a mean concentration of 12.14±8.7 (range, 0.44-31.83) mmol/day, thus showing a slight urinary hypophosphaturia (normal range, 13.0-42.0/day). Of the 16 patients, 10 (62.5%) had significant hypophosphaturia

of 6.74±4.04 (range 0.44-11.0) mmol/day, while the remaining six (37.5%) had normal urinary phosphorus of 21.14±6.5 (range 15.28-31.8) mmol/day.

The distribution of serum alkaline phosphatase (SAP) among our primary hyperparathyroid patients was somewhat skewed (skewedness=1.4288), with a range of 97-2828 U/L (median, 297.50 U/L). The majority of the patients (71%) had SAP (961.35±897; range 171-2818 U/L), well above the normal range (43-154 U/L), while 29% fell within the upper limit of the normal values (122.14±19.0, range 97-147 U/L).

Serum parathormone (PTH) assay results were available in 21 (87.5%) patients. One of them had normal PTH level of 50 pmol/L (5-55 pmol/L) and a serum calcium of 2.8 mmol/L, while the remaining 20 (95%) had a mean value of 317±244.6 (range, 97-870) pmol/L. Three (12.5%) patients in whom PTH was not done had elevated serum calcium (mean 3.20±0.58 mmol/L), low phosphorus (mean, 0.68±0.16 mmol/L), and increased SAP level (1618.33±1286 U/L).

Radiological Investigations

Skeletal survey was not available for all the patients. However, radiological changes in the skeleton, such as brown tumors, subperiosteal bone resorption, salt and pepper appearance of skull, bony deformities and pathological fractures suggestive of hyperparathyroid bone disease, were observed in different combinations in 12 cases (50%).

Dual x-ray absorptiometry (DXA) was performed to measure the lumbar spine (L₂-L₄) and femoral neck BMD in 13 females and one male patient. Based upon the normal lumbar spine BMD in Saudi females (1.143±0.105 g/cm²),⁶ one patient (8%) showed a BMD just below the normal range (1.012 g/cm²), while the remaining 12 (92%) had significantly low BMD (0.744±0.199, range 0.354-0.988 g/cm²), with two of them (17%) showing severe lumbar osteopenia (0.370±0.022, range 0.354-0.385 g/cm²). The mean±SD lumbar spine BMD of all 13 female patients was 0.764±0.204 (range 0.354-1.012) g/cm², thus showing an overall moderate lumbar spine osteopenia in our patients. The single male patient (aged 14 years) had BMD of 0.637 g/cm², which was well below the normal range for Saudi males of his age (0.845±0.202 g/cm²).⁶

Of the 13 females, only two (15%) had normal femoral neck BMD of 0.910±0.005 (range 0.906-0.914) g/cm² (normal female femoral neck BMD, 0.959±0.100 g/cm²),⁵ while the remaining 11 (85%) showed decreased BMD (0.623±0.202, range 0.174-0.795 g/cm²), with two of them having severe femoral neck osteopenia (0.238±0.091, range 0.174-0.303 g/cm²). Moreover, the mean±SD femoral neck BMD in all 13 female patients was considerably less (0.670±0.214, range 0.174-0.914 g/cm²)

than the normal values, thus showing an overall moderate femoral neck osteopenia. The male patient showed a BMD of 0.918 g/cm², which was within the normal range (0.940±0.171 g/cm²) for his age.

Ultrasound examination of the neck was carried out in 12 patients (50%), and parathyroid adenomas could be detected in seven patients (58%, one of them did not have surgery). In the remaining five (42%), ultrasonography showed normal parathyroid glands, which proved to be false-negative after surgical exploration. CT scan of the neck was attempted in only seven patients (29%), of whom six (86%) gave positive results, while one negative study proved false-negative after surgical exploration. Scanning of the parathyroid glands with thallium-technetium subtraction study was performed in 21 patients (88%). Parathyroid adenomas could be detected and located in 18 cases (86%, and three of them did not have surgery), while negative results were obtained in three (14%), which proved to be false-negative after surgical exploration.

A Tc-99m bone scan was available for 23 patients, of whom 11 (47.8%) showed features of metabolic bone disease.

Surgical Findings

Twenty-one (87.5%) of the 24 primary hypertension-parathyroid patients underwent bilateral neck exploration with the excision of abnormal parathyroid (PT) gland(s) and visualization of the remaining normal glands. There were no immediate surgical failures or post-surgical complications in our patients. The final diagnoses, based on surgical and histopathological findings, are outlined in Table 4.

Discussion

Primary hyperparathyroidism has evolved over just three decades from a disease with dramatic presentation to a commonly asymptomatic one in Western countries. One of the major factors behind this change in the trend of presentation is the wide availability of automated chemistry analyzers with routine determination of calcium level. Other factors include a high index of suspicion for the disease and the increase in the number of elderly in the population.¹

Among the first 343 cases reported in 1966 in the Massachusetts General Hospital, 57% had renal stones, 23% had bone disease and fewer than 1% were asymptomatic. Just over three decades later, this presentation is now quite uncommon, with almost half of the diagnosed cases presenting with no symptoms at all.¹ The story is different in Saudi Arabia, where the majority (58%-67%) of our patients present with renal and/or musculoskeletal manifestations. Hypercalcemia was detected in more than 90% of subjects, and SAP, which is a marker of bone activity, was significantly raised in 70% of patients, in keeping with active bone involvement. This

TABLE 4. Parathyroid pathology in patients with primary hyperparathyroidism.

Pathology	N=21 (%)
Parathyroid adenoma	
Single adenoma	18 (85)
Right inferior: 10 (55.5%)	
Left inferior: 5 (28%)	
Right superior: 1 (5.5%)	
Left superior: 2 (11%)	
Multiple adenoma	
Right inferior, left superior	1 (5)
Parathyroid hyperplasia (left inferior)*	1 (5)
Parathyroid carcinoma	
Total	20 (95)
Negative exploration with no pathological confirmation	1 (5)

*Calcium level normalized after parathyroidectomy.

was supported radiologically by the presence of hyperparathyroid bone disease features on plain x-rays in 50% of the patients, which is probably an underestimation in our population, taking into consideration that a full skeletal survey was not done in all cases. More sensitive tests, such as DXA, showed osteopenia of the femoral neck in 79% of patients and lumbar osteopenia in almost all patients, with variable degrees of affection. Bone scan also demonstrated the common involvement of the bone by showing a metabolic bone disease picture in 50% of patients. This is very similar to the Indian experience, which showed a high percentage of skeletal involvement of 95% with florid presentation, which was explained by the common coexistence of vitamin D deficiency.² The Chinese experience in Hong Kong was also similar, with a 74% skeletal involvement.⁷ Renal disease was very common (58%) in our patients, similar to the Indian report (50%),² and higher than the Hong Kong Chinese report of 40% urological manifestations.⁷

At KKHU, routine measurement of serum calcium is not done, however, the prevalence of the disease over the last 16 years has been estimated at 11.34 per 100,000 hospital admissions, which might be an underestimation, because other studies have already reported increases in the number of primary hyperparathyroidism cases detected after the introduction of routine serum calcium analysis.^{1,7} Other hospitals in Saudi Arabia do include calcium level in their routine chemistry analysis, but so far we do not know of the prevalence of primary hyperparathyroidism in these institutions.

Heath¹ showed a marked increase in the annual incidence from 7.8±1.2 (mean±SD) cases per 100,000 population before the introduction of routine measurement of serum calcium in 1974 to an average annual incidence of 51.1±9.6 cases per 100,000 population after the availability of this test, thereby exhibiting a dramatic increase in the incidence of the disease pick-up during routine screening. This incidence later on stabilized to 27.7±5.8 cases annually. In Hong Kong Chinese,⁷ the prevalence of the disease in a major university hospital increased from 3.1 to 3.7 per 100,000 hospital population.

Interestingly, almost 60% of our patients were above the age of 40 years, similar to the Western experience,⁸⁻¹⁰ but contradicting the Indian report, where 68% of the patients were below the age of 40.¹¹ Women showed a higher ratio of 7:1 to men, and a mean age of 46 years at presentation, which is similar to the Western experience.¹

Of the various imaging techniques used for the preoperative localization of parathyroid adenoma, the thallium-technetium subtraction study exhibited the highest sensitivity of 83%, which is in agreement with other reports in the literature.^{12,13,14} High-resolution USS of the neck in our patients had a sensitivity of 54.5%, which is similar to figures quoted in the literature.¹² Other studies have cited higher or lesser degrees of sensitivity.¹³⁻¹⁶ Some investigators have proposed combining USS and the subtraction study for a higher sensitivity.^{12,14}

CT scan of the neck was performed in only one-third (29%) of the patients, with a sensitivity of 86%, which is comparable to the reported sensitivity of 41%-86% in the literature.^{12,16,17}

It has been argued by many authorities that preoperative localization is not necessary, as the success rate of parathyroid gland identification and removal approaches 95% in the hands of a good surgeon.^{18,19} In our study, 95% of the cases underwent successful parathyroidectomy of the diseased gland(s). There was only one patient with negative exploration and no histopathological confirmation of the disease. None of the patients experienced any post-surgical complications. Single parathyroid adenoma was found in 85% of the subjects, while multiple adenomas (two) were encountered in around 5% of the studied population. Our findings are comparable to those reported in many other countries, with an incidence of 80%-87% single PT adenoma.^{7,11,19,20,21} However, the occurrence of right inferior PT adenoma in a considerably higher proportion (55.5%) of our patients does need further explanation. There were no cases of parathyroid carcinoma.

In conclusion, primary hyperparathyroidism is a disease with serious complications and major morbidity and cost to the community. It is a common disorder in the Western countries and a fairly common one in Asia. In Saudi Arabia, the prevalence is probably underestimated, especially in areas where routine serum calcium analysis is not performed. The majority of patients present late with symptomatic skeletal and/or renal complications and, therefore, routine screening for serum calcium is warranted to avoid the serious late complications of untreated hypercalcemia. Of course, this leads us to the controversial question of how best to treat asymptomatic hyperparathyroidism. In the consensus development conference held in the US in 1991,²² guidelines were devised addressing this problem in order to minimize the risk of complications.

Primary hyperparathyroidism, with its diverse presentations and potential complications, is still a

challenging disease for physicians and surgeons alike. There is no simple formula that addresses all types of patients presenting with this disorder, but definite treatment remains to be the surgical removal of the diseased parathyroid gland(s). However, factors like age, symptomatology, presence of other diseases, and indications and contraindications for surgical intervention should be taken into consideration before the initiation of therapy.

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