

PRIMARY HYPERPARATHYROIDISM AND VITAMIN D DEFICIENCY: A COMBINATION STILL ENCOUNTERED IN ASIAN COUNTRIES

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Primary hyperparathyroidism is characterized by inappropriately excessive production of parathormone with subsequent hypercalcemia, hypophosphatemia, and normal to high serum alkaline phosphatase. The serum 1,25 dihydroxycholecalciferol is either normal or frequently higher than normal because of accelerated conversion of 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol by high levels of circulating parathormone.¹ When the serum alkaline phosphatase is significantly elevated, indicating ineffective mineralization of osteoid, especially in the presence of normal or slightly high serum calcium levels, one should consider the possibility of a coexisting vitamin D deficiency state.

The combination of primary hyperparathyroidism and vitamin D deficiency is seldom reported in the literature, especially in Western countries, but it has been the experience of some Asian countries, particularly the Indian subcontinent and China, that this combination is not as rare as previously thought.^{2,3} This report describes our experience with the coexistence of primary hyperparathyroidism and vitamin D deficiency at a major teaching hospital and tertiary health center in Saudi Arabia, and attempts to review the literature.

Patients and Methods

Over a period of 16 years from 1982 until December 1997, 24 cases of documented primary hyperparathyroidism were identified from the centrally computerized system of patients medical records at King Khalid University Hospital (KKUH), one of the large tertiary care hospitals in Riyadh City, Saudi Arabia. Of these 24 cases, five were of documented primary hyperparathyroidism associated with vitamin D deficiency. KKUH is a large prestigious teaching institution managing over 300,000 outpatients and over 24,000 admissions per year. It is one of the seven major healthcare centers in Riyadh, which serves a community of about 2.6 million residents.

The medical records of the five documented primary hyperparathyroidism patients were retrospectively reviewed for age, sex, marital status, growth parameters, previous medical history, presenting signs and symptoms, routine biochemical investigations, histopathological diagnosis and radiological findings. The diagnosis of primary hyperparathyroidism was based on one or more of the following criteria: 1) histological evidence (after parathyroidectomy) of a parathyroid adenoma; 2) persistent elevation of serum calcium above the upper limit of normal range of 2.60 mmol/L, excluding other demonstrable cause of hypercalcemia; and 3) increased circulatory immunoreactive parathyroid hormone (PTH), above the upper limit of normal range of 50 pmol/L, along with pathognomonic radiographic features. The diagnosis of vitamin D deficiency was based on the presence of the following criteria: 1) low circulatory 25 hydroxycholecalciferol (25-OHD₃) (<20 ng/dL), since it is a more stable and reliable indicator of vitamin D status in an individual; and 2) high serum alkaline phosphatase (SAP) (>150 UI/L) indicating marked osteoblastic activity, along with pathognomonic radiological features of osteomalacia. Daily 24-hour renal excretion of calcium and phosphorus were used as additional helpful tests and to complete the biochemical profile of the patients studied.

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 2.12-2.6 mmol/L for serum calcium (Ca), 0.8-1.40 for serum phosphorus, 43.0-154 U/L for serum alkaline phosphatase (SAP), 2.5-7.5 mmol/day for urinary calcium, and 13-42 mmol/day for urinary phosphorus. The serum PTH and 25-OHD₃ radioimmunoassay were performed at Bioscientia Laboratories, Germany, with the normal range being 5-50 pmol/L for PTH, and 20-120 ng/mL for 25-OHD₃.

Radiological investigations included one or more of the following: skeletal survey, USS of the neck, parathyroid scan (Thallium-Technetium subtraction study), CT scan of the neck, bone scan (T99M scan), and bone mineral densities (BMD) of femoral neck, lumbar and spine (L₂ - L₄) by dual x-ray absorptiometry (DXA). Peak BMD in normal Saudi population, aged 20-40 years, have been found to be almost equal in both males and females, with a mean BMD of 1.42±0.096, and 1.143±0.105 for L₂-L₄ and

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1.036±0.137 and 0.959 ± 0.100 for the femoral neck,⁴ respectively.

Results

Table 1 shows the clinical characteristics of the five patients. There was a preponderance of females, with a 4:1 ratio over males. The mean±SD age of the four female patients was 38.5±5.9 (36-47) years, while the single male was 28 years old.

Table 2 outlines the symptoms and signs of the patients. Musculoskeletal symptoms were common, ranging from 40%-60%, while a history of renal calculi was obtained in 60% of cases. Symptoms of hypercalcemia in the form of polyuria and polydipsia were seen in 40% of patients. None of the patients presented with gastrointestinal disturbances such as constipation, nausea or vomiting, and there were no documented cases of neuropsychiatric disturbances.

Table 3 shows the biochemical profile of the patients. All patients had elevated serum calcium and low phosphorus. Serum alkaline phosphatase (SAP) was raised in four patients, with the male having a value of 346 U/L and the females a median value of 413 U/L (101-2007). One female patient (20%) had a normal SAP of 101 U/L. The median of the four patients with high SAP was 496 (180-2007).

The 24-hour urinary calcium was reported within normal limits (2.5-7.5 mmol/L) in three female patients, with a mean value of 4.5±1.27 (3.7-6) mmol/day, while the male patient had hypercalcuria with a concentration of 25 mmol/day. The 24-hour urinary phosphorus was not

reported in the male patient. Of the three female patients, two had below normal while one had normal urinary phosphorus, with a total mean concentration of 12.3±2.4 (10.9-15.2) mmol/day.

Radiological Investigations

A complete skeletal survey was not available for all patients. Two females (40%) had classical features of primary hyperparathyroid bone disease with subperiosteal bone resorption, salt and pepper skull appearance, brown tumors and pathological fractures. One female and the single male patient had some features of bone involvement with subperiosteal bone resorption and skull changes, thus making an almost 80% involvement of bones secondary to primary hyperparathyroidism. A bone scan was available for two (40%) female patients, and showed a super scan of severe metabolic bone disease.

DXA was not available for the male patient and was reported only in three (60%) female patients. The L₂-L₄ BMD was 0.890±0.12 (0.76-0.988) g/cm², showing significant reduction below the normal range of 1.143±0.105 g/cm². One of the three patients showed severe osteopenia with a BMD of 0.76 g/cm². DXA of the femoral neck showed significant osteopenia, with a BMD of 0.723±0.05 (0.686-0.77) g/cm², which was far below the normal value of 0.959±0.100 g/cm².

USS of the neck was done in three patients, with two (67%) of them showing positive results and the localization of a single parathyroid adenoma. Parathyroid scan was attempted in three patients, with positive localization of a single parathyroid adenoma in all (100%) of them. Four patients, three female and the single male, had parathyroidectomy with identification of a single adenoma and its removal with histopathological confirmation of the diagnosis.

Discussion

Primary hyperparathyroidism is a relatively common disease in the Western countries, with an estimated annual incidence of 28 per 100,000 population in the USA.⁵ In Saudi Arabia, a limited study conducted at a major university hospital showed a prevalence of 11.34 per 100,000 population.⁶ Vitamin D deficiency or osteomalacia in adults is becoming rare in the West, with the improvement in nutritional status and fortification of dairy products as well as the public awareness of the benefit of limited sun exposure. In many Asian countries, vitamin D deficiency remains a common health problem,² which is also encountered in the immigrants of these populations in Western countries.^{7,8}

Vitamin D deficiency commonly leads to a secondary hyperparathyroidism, which is a compensatory phenomena triggered by the low circulating calcium levels acting on the specific calcium receptors on the parathyroid cells to stimulate overproduction of PTH. This helps to bring the

TABLE 1. Demographics of five patients with primary hyperparathyroidism and vitamin D deficiency.

Variable	Male	Female	Total
Sex	1	4	5
Age (yrs) mean±SD (range)	28	38.5±5.9 (34-47)	36.4±6.9 (28-47)
BMI mean±SD (range)	22	24.36±5.4 (18.1-28)	23.77±4.6 (18.1-28)
Nationality			
Saudi	1 (25%)	2 (75%)	3
Non-Saudi	-	2 (100%)	2

TABLE 2. Clinical presentation of patients with primary hyperparathyroidism and vitamin D deficiency.

Symptoms	Number (%)
Generalized weakness	3 (60)
Proximal muscle weakness	2 (40)
Joint pain	3 (60)
Bone pain and aches	3 (60)
Generalized body ache	1 (20)
Polyuria	2 (40)
Polydipsia	2 (40)
Renal calculi	3 (60)

serum calcium level back to normal by virtue of mobilizing calcium from its stores in the bones and increasing intestinal absorption.⁹ In partial or mild forms of vitamin D deficiency, this mechanism successfully brings the calcium level back to normal. In severe untreated forms of osteomalacia on the other hand, this mechanism fails and subsequently leads to the classical biochemical features of vitamin D deficiency in the form of hypocalcemia, hypophosphatemia, and high SAP due to ineffective mineralization of osteoid.

The combination of primary hyperparathyroidism and vitamin D deficiency is rare. Over the last three decades, only a few cases have been reported in the Western literature.¹⁰⁻¹² In Asia, however, many studies have shown that the two diseases can coexist. One such study from India² in 1995 showed that 50% of the patients with hyperparathyroidism were normocalcemic, and that all the patients in the study were vitamin D deficient, which probably explained the high ratio of normocalcemia in their hyperparathyroid population and accounted for the severe skeletal involvement. The Chinese experience is also similar, with Meng³ in 1990 reporting 51.6% of his patients having primary hyperparathyroidism in combination with osteomalacia.

Many skeptical authorities have attempted to explain the coexistence of this combination, claiming that the parathyroid adenoma is due to tertiary hyperparathyroidism in the face of chronic hypocalcemia,¹³⁻¹⁶ while others suggest that a deficiency or absence of a calcium-binding protein (CaBP) in the parathyroid tissues account for the high rate of PTH overproduction after normalization of calcium level or even in the face of hypercalcemia.¹⁷

On the other hand, the combination of primary hyperparathyroidism and vitamin D deficiency has been a recognized entity in many Asian countries. In Saudi Arabia, vitamin D deficiency is a common disease,¹⁸⁻²⁰ as is primary hyperparathyroidism,⁶ so the co-existence of the two diseases in the same patient, even though uncommon, could be encountered and probably more than in developed countries.

Our current study revealed the presence of five such cases at a major teaching hospital over a period of 16 years. The majority (40%-60%) of the patients presented with musculoskeletal complaints, and about 40% with renal calculi. They all had hypercalcemia and severe hypophosphatemia. In four patients, the presence of a parathyroid adenoma was confirmed by histopathological examination of the excised parathyroid gland after neck exploration, while the fifth case had a parathyroid scan and USS examination confirming the presence of a single parathyroid adenoma, but the patient declined surgery.

There were five more patients who were suspected to have this combination based on the presence of very high SAP values in all of them, and radiological features of osteomalacia in some of them, but unfortunately data on

vitamin D levels were lacking and, therefore, could not be included in this study.

Primary hyperparathyroidism could either contribute to or unmask a subclinical vitamin D deficiency. Many theories have been postulated for the occurrence of these two diseases together. Albright and Reifenstein¹³ and Nordin,²¹ in the middle of this century, suggested that osteomalacia may result when the calcium phosphorus product falls below 25 in adults (using mg/dL units). This was further supported by Kaplan et al.¹⁰ in their report in 1988, indicating that severe hypophosphatemia is the major culprit. In 1971, Woodhouse et al.²² postulated that vitamin D deficiency ensues in primary hyperparathyroidism, with overproduction of PTH, accelerating the conversion of 25-OHD₃ to 1,25-OHD₃, therefore depleting the body stores of vitamin D metabolites. They also suggested that in primary hyperparathyroidism a vicious cycle may be created, with vitamin D deficiency further increasing the PTH level.

The coexistence of primary hyperparathyroidism and vitamin D deficiency is probably a multifactorial pathology, with the chronic hypophosphatemia being induced by the hyperphosphaturic effect of PTH on the renal tubules, as well as the induced vitamin D deficiency secondary to the accelerated conversion of 25-OHD₃ to the active 1,25-OHD₃, depleting the vitamin D stores, both contributing to poor mineralization of the bone and ultimately leading to osteomalacia. The latter explanation plays a more prominent role in patients with pre-existing borderline vitamin D stores, or those with deficiency due to nutritional causes, lack of sun exposure or other causes of

TABLE 3. Biochemical profiles of patients with primary hyperparathyroidism and vitamin D deficiency.

Variable	Reference range	#	Concentration mean±SD		
			Male	Female	Total
Serum calcium	2.12-2.6 mmol/L	5	3.72 (1)	2.86±0.18 (2.64-3.04)	3.03±0.41 (2.64-3.72)
Serum phosphorus	0.8-1.40 mmol/L	5	0.66 (1)	0.64±0.09 (0.58-0.75)	0.65±0.07 (0.58-0.75)
SAP	43-154 U/L	5	346 (1)	413 (101-2007) (4)	346* (101-2007)
PTH	5-50 pmol/L	5	507 (1)	370±345 (122-870) (4)	397±305 (122-870)
25-OHD ₃	20-120 ng/mL	5	<10 (1)	<10 (4)	<10
Urinary calcium	2.5-7.5 mmol/day	4	25 (1)	4.54±1.27 (3.7-6) (3)	5* (3.7-25)
Urinary phosphorus	13-42 mmol/day	3	-	12.3±2.4 (10.9-15.2) (3)	12.3±2.4 (10.9-15.2)

*Median value, SAP=serum alkaline phosphatase; PTH=parathyroid hormone.

vitamin D deficiency. The possibility of a subclinical form of vitamin D deficiency being unmasked later after the occurrence of primary hyperparathyroidism can operate in many cases, particularly in areas where vitamin D supply is deficient, such as in Asian communities.

In many Asian countries, including Saudi Arabia, vitamin D deficiency is a common disorder and, therefore, should always be suspected in patients with primary hyperparathyroidism who exhibit features of a coexisting vitamin D deficiency, such as normal or near normal serum calcium levels, high SAP, and clinical or radiological features of osteomalacia. The daily urinary excretion of calcium and phosphorus might give additional helpful clues. In the presence of normal renal function, normal or low phosphorus excretion in the face of high serum PTH and significant hypophosphatemia suggests vitamin D deficiency. Also, the presence of low or normal urinary excretion of calcium with high serum PTH and hypercalcemia might indicate poor calcium mobilization from the intestine and bone due to vitamin D deficiency and, therefore, PTH-dependent calcium reabsorption is mainly through the kidney. Only when this exceeds the renal adaptive mechanism does significant hypercalcuria occur, as was observed in our male patient.

It is important to pay attention to this particular entity because of the severe skeletal involvement encountered and the risk of severe hungry bone syndrome following surgical resection of the parathyroid adenoma.

The bones are usually very deficient in their stores of calcium and phosphorus and once the autonomus gland is resected, a severe form of hypocalcemia can ensue with complications if the patient is not promptly and adequately treated. Two of our female patients had the severe form of hungry bone syndrome, which necessitated large amounts of intravenous calcium infusion for a few days postoperatively. Such patients will require oral supplementation with calcium and vitamin D for some time postoperatively to replenish their stores and should be followed up regularly with biochemical profiles and radiological assessment.

In conclusion, primary hyperparathyroidism and vitamin D deficiency is common in many Asian countries, including Saudi Arabia. We believe that most of the patients with this combination start with either unrecognized forms of vitamin D deficiency or a subclinical state which worsens with the development of the primary hyperparathyroidism. The possibility of the primary hyperparathyroidism itself leading to vitamin D deficiency in the long term is plausible, but since the latter disease is prevalent in Asian communities, it would appear that the vitamin D deficiency state predates the development of the primary hyperparathyroidism, which leads to worsening of the former. Awareness of this combination is important for the adequate preparation of the patient before surgery and after surgical removal of the diseased parathyroid gland(s).

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