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Assessment and Therapy of Five Hundred Five Patients With Primary Hyperparathyroidism

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Abstract

Background: The aim of the study was to assess the clinical, biochemical, hormonal, and pathological findings in 505 patients with primary hyperparathyroidism (PHPT).

Methods: Three hundred seventy-four females and 131 males with PHPT were enrolled in this study. Studies include a blood chemistry profile and serum phosphorus, parathyroid hormone (PTH), 25-OHD and 1,25-OHD levels, a 24-h urine collection for measurement of creatinine, calcium, and phosphorus, dual energy X-ray absorptiometry (DXA) studies of lumbar spine, hip and forearm, and pathological findings in 253 patients who had surgery. Standard descriptive analyses were utilized for assessment of data.

Results: All patients had persistent or intermittent hypercalcemia except for three with normocalcemic PHPT. With the exception of a family with the multiple endocrine neoplasia type 1 (MEN1) disorder and another family with familial isolated PHPT, patients had sporadic PHPT. Hypercalciuria was present in patients with and without urolithiasis. Serum PTH levels were increased or normal and unsuppressed in all patients. Twenty-six percent of patients had hypophosphatemia and 70% had subnormal TmP/GFR (tubular maximum for phosphate reabsorption per unit of glomerular filtrate) values. Serum 25-OHD levels were subnormal in 73% of patients and serum 1,25-OHD levels were increased in 23% of patients. DXA measurements in 59% of patients revealed the lowest scores at the one-third radius site. Of the 253 patients who had surgery, 84% had a single adenoma, 14% had multiglandular disease, and 2% had carcinoma.

Conclusions: PHPT continues to be a common sporadic endocrine disorder especially in women. Classical parathyroid-related disorders were present in less than half of patients while there was a greater number of patients with a variety of non-traditional disorders and complaints. Ninety-two percent of patients had mild hypercalcemia, and many had hypercalciuria, subnormal 25-OHD levels, hypophosphatemia, excess phosphorus excretion, and DXA data that revealed a greater loss of cortical bone. Surgery in patients with traditional or classical target disorders generally resulted in clinical improvement whereas successful surgery in patients with non-classical target disorders had variable clinical responses with many not exhibiting an appreciable change in quality of life.

Keywords: Hyperparathyroidism; Hypercalcemia; Hypophosphatemia; Urolithiasis; Osteoporosis

Introduction

Primary hyperparathyroidism (PHPT) was first described in the 1920s and 1930s as a rare disease associated with bone and stone problems and symptoms such as moans and groans in the United States and in Austria [1, 2]. In subsequent years it became evident that it was a more common endocrine disorder with a prevalence of 2 to 3 in 1,000 females and 1 in 1,000 males [3], characterized by hypercalcemia due to an increase in serum parathyroid hormone (PTH) or an inappropriately normal or non-suppressed PTH level [4]. With the general availability in the 1970s of blood chemistry profiles, hypercalcemia, the *sine qua non* of PHPT at that time, was being found in many asymptomatic patients [5]. More recently, patients with both normal total and ionized serum calcium levels have also been diagnosed with PHPT [6]. For the past 50 years the Division of Endocrinology and Metabolism at the Roger Williams Medical Center has been involved in the evaluation and therapy of many patients with skeletal, renal, and mineral disorders. This report represents a review of the clinical, biochemical, and hormonal findings in 505 patients with PHPT, including the pathological and surgical findings in 253 of these patients that thus far have had parathyroid surgery.

Materials and Methods

Patients with an ultimate diagnosis of PHPT were referred to the author for evaluation of an elevated serum calcium level or in many cases for a history of hypercalcemia for varying time periods. The author obtained a complete medical history and physical examination of all the patients in this study and ordered the appropriate studies and examinations that would

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ultimately document a diagnosis of PHPT. Patients include 374 females and 131 males in keeping with 2.9 times as many females as compared to males. Most of the patients have had sporadic PHPT and this includes four males and two females with ages of 16 to 20 years with no family history of PHPT. There was one family with documentation of the multiple endocrine neoplasia type 1 (MEN1) disorder with three brothers who had PHPT, and another family with three brothers with familial isolated PHPT. Three women had normocalcemic PHPT. Studies have included a chemistry profile, serum phosphorus, serum PTH, and in more recent years serum 25-OHD, and 1,25-OHD levels. Serum PTH measurements were obtained in all of the patients and through the years there has been a number of PTH assays with progression to second and third generation assays. The 24-h urine collections were obtained for measurement of creatinine, calcium and phosphorus and these measurements have allowed for the calculation of creatinine clearances, urine calcium excretion, urine calcium/creatinine (Ca/Cr) ratios, and urine TmP/GFR (tubular maximum for phosphate reabsorption per unit of glomerular filtrate) values. Preoperatively patients have had parathyroid sestamibi scans and/or sensitive ultrasound studies. Parathyroid venous sampling and arteriography were necessary many years ago to uncover in one patient a functioning mediastinal lesion. Since the 1990s Hologic dual energy X-ray absorptiometry (DXA) studies at this unit have been obtained of the lumbar spine, hip, and one-third radius site. Generally, renal ultrasounds have been obtained by urologists caring for some of these patients with calcium stone disease or by this unit. Standard descriptive analyses were applied to the clinical, biochemical, hormonal, pathological, and DXA data and two sample *t*-tests for assessment of biochemical data.

The Institutional Review Board (IRB) approval was obtained. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Mean age for all of the patients was 60.9 ± 0.6 with an age range of 16 to 96 years. Mean age of the males was 56 ± 1.4 years with a range of 17 to 88 years while mean age for the females was 62.6 ± 0.7 years with an age range of 16 to 96 years. Peak incidence of PHPT was in the sixth decade for both males and females. In patients less than 45 years of age there were 30 females (16 - 44 years of age) and 29 males (19 - 42 years of age). Mean body mass index (BMI) value (kg/m^2) for 396 patients with such measurements was 28.5 ± 0.3 with a range of 17 to 57 (normal values 20 - 25, overweight 25 ≤ 30, obesity 30 or greater). In keeping with parathyroid-related traditional or classical target disorders that are directly related to PTH and/or hypercalcemia, three patients had osteitis fibrosa cystica, 20% of patients had a history of kidney stone disease, 21% had osteoporosis, and 6% of patients had both stone disease and osteoporosis. Eleven percent of patients were asymptomatic with no complaints or disorders. Sixty-eight percent of patients, including many with stone disease and osteoporosis, had one or more non-classical manifestations that have been described in patients with asymptomatic PHPT in the literature. Eight patients had Paget's disease of bone. Thirty-four percent of patients had hypertension, 18% had a history of depression, anxiety, or other psychological problems, 20% had a history of weakness, fatigue and/or weariness, and 21% had a history of constipation, abdominal discomfort, gastritis, history of peptic ulcer disease or pancreatitis. One hundred forty of 396 patients with BMI measurements had obesity (36%). There were 15 patients with a history of cognitive abnormalities and other central nervous system (CNS) problems.

Mean serum calcium for the entire group of patients was 11.2 ± 0.04 mg/dL with a range of values of 10.0 to 15.6 mg/dL (normal range 8.5 - 10.5 mg/dL). Within a 6 to 24 months' period prior to or during our studies and evaluation, an occasional or intermittent normal serum calcium level was evident in 66 patients (13%). Mean serum calcium levels were similar at 11.1 mg/dL in those with and without obesity. Most patients had mildly elevated serum calcium levels up to 12 mg/dL, while 37 patients had moderate hypercalcemia with serum calcium levels varying from 12.1 to 13.7 mg/dL. Five patients had severe hypercalcemia with levels of 14.1 to 15.6 mg/dL. Mean serum albumin level of the whole group was 4.3 ± 0.02 g/dL with a range of values of 2.8 to 5.3 g/dL. In the entire group, all but 10 patients had normal serum albumin levels. In nine of the 10 patients with hypoalbuminemia, serum calcium levels were elevated varying from 10.6 to 13.7 mg/dL, while one patient had a serum calcium of 10.1 mg/dL, but when corrected for the serum albumin, the calcium level was increased at 10.9 mg/dL. There were three patients with PHPT with normal serum calcium, albumin, and ionized calcium levels, in keeping with normocalcemic PHPT.

For the entire group mean 24-h urine calcium excretion was 250 ± 7 mg. Mean urine Ca/Cr ratio was 0.24 ± 0.01 with a normal range of 0.05 - 0.25. Forty percent of females had hypercalciuria with 24-h urine calcium excretion greater than 250 mg and 33% of males had calcium excretion greater than 300 mg. Thirty-one percent of patients had urine Ca/Cr ratios greater than 0.25. Seventy percent of patients with an increase in 24-h urine calcium excretion had an increase in Ca/Cr ratios. Twenty percent of patients had a history of urolithiasis which included 64 females and 30 males. Forty of the 64 females (63%) with a urolithiasis history had 24-h urine calcium excretion greater than 250 mg, and 10 of the 30 males (33%) with a history of urolithiasis had 24-h urine calcium excretion greater than 300 mg. Interestingly, 33% of females without a history of urolithiasis had urine calcium excretion greater than 250 mg, and 9% of males without a urolithiasis history had 24-h urine calcium excretion greater than 300 mg/24 h.

Mean serum phosphorus level was 2.8 ± 0.02 mg/dL (normal range 2.5 - 4.5 mg/dL) with levels varying from 1.1 to 4.5 mg/dL. One hundred twenty-nine patients (26%) had hypophosphatemia with levels below 2.5 mg/dL, and another 47 patients (10%) had low normal serum phosphorus levels of 2.5 mg/dL. Excess phosphorus excretion was evidenced by a mean TmP/GFR value of 2.1 ± 0.03 mg/dLGF with a normal range of values of 2.5 - 4.2 mg/dLGF. Seventy percent of patients had TMP/GFR values less than 2.5 mg/dLGF.

Through the years various serum PTH assays were used in assessing patients. This has included radioimmunoassays for mid and carboxy regions of PTH, intact PTH assays, and

in more recent years intact PTH measurements as assessed by second and third generation assays. Overall, 78% of patients had increased serum PTH levels, and 22% of patients had normal or non-suppressed levels, in keeping with a diagnosis of PHPT.

Mean serum 25-OHD level in 326 patients with such measurements was 22.8 ± 0.6 ng/mL, with a range of values of 5 to 58 ng/mL. Serum 25-OHD levels were normal in 87 of the 326 patients (27%), with a mean value of 37 ± 0.9 ng/mL and range of values of 30 to 58 ng/mL. Two hundred thirty-nine patients had serum 25-OHD levels less than 30 ng/mL (73%). Ninety-seven patients had levels between 20 and 29 ng/mL (30%), 119 patients had serum 25-OHD levels between 10 and 19 ng/mL (37%), and 23 patients had levels less than 10 ng/mL (6%). Serum 25-OHD levels were less than 30 ng/mL in 95 of 141 patients (67%) with obesity, with a mean value of 18 ± 0.7 ng/mL and a range of 6 to 28 ng/mL. Serum 25-OHD levels were less than 30 ng/mL in 131 of 255 patients (51%) with normal BMI values, with a mean serum 25-OHD level of 19 ± 0.5 ng/mL, and a range of values of 5 to 29 ng/mL. Mean serum 1,25-OHD level in a total of 339 patients was 58 ± 1.3 pg/mL, with a range of values of 10 to 150 pg/mL (normal range 18 - 72 pg/mL). Serum levels greater than 72 pg/mL were present in 79 patients (23%). Three of five patients with subnormal 1,25-OHD levels from 8 to 17 pg/mL had low serum 25-OHD levels of 18, 21, and 23 ng/mL, respectively.

In the 300 patients that had DXA studies of spine, hip, and forearm, the lowest T-scores were evident at the one-third radius site in 59% of patients. Of those with osteoporotic readings, the lowest values were present at the one-third radius site in 74 of 95 studies (78%).

For many years the standard surgical approach was that of four gland exploration but in recent years many patients have had a minimally invasive procedure following ultrasound and/or sestamibi scans. Also, before and after removal of a lesion or lesions, blood specimens in recent years have been obtained for measurement of PTH levels for documentation of a significant drop in serum PTH. Of the 253 patients who had surgery, one had unsuccessful surgery, another had successful surgery without a pathologic specimen, one patient died during surgery due to a myocardial infarction, and in two cases pathologic data with successful surgery were not available. A single adenoma was found in 209 patients (84%), multiglandular disease in 34 patients which included 20 with two adenomas and 13 with hyperplasia (14%). There were four patients with oxyphil adenomas. Functioning oxyphil adenomas were resected in two patients and in a third patient an oxyphil and chief cell adenoma was resected. A fourth patient had resection of an oxyphil adenoma from the neck that failed to drop the serum calcium level to normal. Subsequent arteriography and venous studies indicated a second tumor in the mediastinum, which interestingly was another oxyphil adenoma; but its resection resulted in normalization of serum calcium levels. There were four patients with parathyroid carcinoma (2%) and one lesion was intrathyroidal. Two patients each had a mediastinal adenoma, three patients each had a posterior esophageal adenoma, and one had an intrathyroidal adenoma. When adenomas were localized in surgical reports, 110 adenomas were inferior lesions and 56 were upper lesions. Mean weight of the adenomas was 1,074 ± 103 mg with a range of weights of 50 to 9,750 mg. Two females and two males had parathyroid carcinoma (2%). Two of the lesions weighed 1,500 mg, a third 1,600 mg, and the fourth 2,000 mg. The female patients were 36 and 52 years of age and the males were 52 and 60 years of age. Serum calcium levels in these patients were 10.8, 12.9, 13.0, and 11.9 mg/dL, respectively. At the time of surgery seven cases of thyroid carcinoma were discovered including six cases that were papillary and one that was a follicular carcinoma.

Discussion

This retrospective review of 505 patients with PHPT reaffirms that women are more affected than males with a 2.9:1 ratio compared with a ratio of 3 - 4:1 reported in the literature [7, 8]. With the exception of a family with several siblings with the MEN1 syndrome and another family with several siblings with isolated familial PHPT, the disease has been of sporadic variety. Peak incidence of PHPT has been reported to be in the sixth or seventh decade of life [9, 10]. The highest incidence rate of PHPT has been reported in females of 65 - 74 years of age [11]. In this series peak incidence occurred in the sixth decade in 123 females and 38 males. According to Wermers et al [11], prior to 45 years of age the incidence of PHPT in females and males was comparable. In the present series of the patients less than 45 years of age, there were 30 females and 29 males.

Regarding the concept of asymptomatic PHPT defined as those without osteitis fibrosa cystica, renal stones, renal related problems, or osteoporosis, most patients with PHPT are in this category [3, 12-14]. Eleven percent of patients were indeed asymptomatic but many other patients with asymptomatic PHPT did have a variety of non-traditional or non-classical target disorders and related symptoms that have not been definitively related to PHPT [3, 13, 14]. Osteoporosis and both cortical and trabecular bone loss and an increased fracture risk have been reported in many patients with PHPT [3, 14-17]. Interestingly, two reports have indicated that less than 5% of patients with PHPT had bone disease [18, 19]. In the present series 21% of the patients did have osteoporosis. In keeping with the literature [14], DXA studies in our patients revealed greater reductions at the one-third radius site as compared with the lumbar spine and hip. Also, 20% of patients had a history of kidney stone disease and 6% of patients had both stone disease and osteoporosis.

The PHPT literature is replete with most patients having mild hypercalcemia with levels of 10.5 to 11.9 mg/dL [3, 12, 13]. In the present series, serum calcium levels in most patients were mildly increased to 12 mg/dL. Thirty-seven patients had moderate hypercalcemia with serum calcium levels of 12.1 to 13.7 mg/dL. Five patients had severe hypercalcemia that ranged from 14.1 to 15.6 mg/dL. In the few patients that had hypoalbuminemia, serum calcium levels were elevated except for one patient with a serum calcium of 10.1 mg/dL and a serum albumin of 3.1 g/dL. When corrected for albumin the serum calcium level was increased at 10.9 mg/dL. Interesting is the observation in this study of an occasional or intermittent normal serum calcium level in 13% of patients. Documentation of normocalcemic PHPT was made in three patients who consistently had normal

serum total and ionized calcium levels with no secondary causes for the elevated serum PTH levels. Two of these patients did have surgery including one who was reported with progressive cortical bone loss over a 7-year period [20].

Increased urine calcium excretion and nephrocalcinosis have been reported in up to 30% of patients with PHPT and stone disease in up to 20% of patients [21]. Insogna [13] has indicated that 24-h urine calcium measurements can aid in assessing the risk of stone formation. According to Peacock [22], however, a 24-h urine calcium measurement is of limited value. He stated that stone disease is multifactorial and that an increase in calcium excretion is only one of several underlying factors such as abnormalities in oxalate and citrate excretion and a more alkaline urine. In the present series in agreement with the literature, there was a history of urine stone disease in 20% of patients. Forty of 64 females (63%) with a history of stone disease had urine calcium excretion greater than 250 mg. Ten of 30 males (33%) with such a history had urine calcium excretion greater than 300 mg. Interestingly, 102 females (33%) and 23 males (9%) with PHPT without stone disease had similar increases in calcium excretion to greater than 250 mg in females and to greater than 300 mg in males, respectively. Generally, idiopathic calcium stone disease has been more common in males, but in PHPT there has been a similar prevalence in females and males [22]. In the present series, however, there were almost two times as many females as males with a history of calcium stone disease.

Lafferty [23] reported that serum phosphorus levels were low in severe PHPT and low normal in milder forms of PHPT. Silverberg et al [21] reported that serum phosphorus levels are usually in the lower range of normal and below normal in one-third of patients. Clarke [3] has indicated that in both symptomatic and asymptomatic patients with PHPT serum phosphorus levels are usually low normal or mildly decreased. Insogna [13], however, has reported that in PHPT serum phosphorus levels are normal or low normal. In the present series the mean serum phosphorus level was normal at 2.8 mg/dL. However, 129 of 505 (26%) had hypophosphatemia and 47 other patients had low normal serum phosphorus levels. As indicated by Peacock [22], the decrease in renal phosphorus reabsorption in PHPT is attributed to an increase in both PTH and fibroblast growth factor-23 (FGF-23). In the present series the low TmP/GFR levels in 70% of patients document excess phosphorus excretion, and as suggested by Peacock [22], this supports and corroborates the diagnosis of PHPT.

Boudou et al [24] reported a very high incidence of low serum 25-OHD levels in patients with PHPT. Clarke [3] has indicated that serum 25-OHD levels are usually low normal in asymptomatic PHPT; and Insogna [13] has stated that serum levels of 25-OHD are normal or low normal in patients with PHPT. According to Silverberg et al [21] serum 25-OHD levels tend to be in the lower end of the normal range of values, and that less vitamin D deficiency is now likely due to supplementation with vitamin D, as reported by Walker et al [25]. In a longitudinal natural history study of patients with mild PHPT enrolled in the 1980s and 1990s, serum 25-OHD levels were below 20 ng/mL in 53% of patients, and 80% of patients had values below 30 ng/mL [26]. Interestingly, for years there had been reluctance to restore 25-OHD levels to normal in patients with PHPT due to concern of adverse effects on serum calcium and urine calcium excretion. Subsequent data relating to vitamin D therapy in patients with PHPT indicated no evidence of adverse effects on serum calcium or urine calcium excretion [27, 28]. Bouillon et al [29] have indicated that low serum 25-OHD levels are common in PHPT and have suggested that the underlying factor for this finding is related to the effect of PTH on increasing the metabolism and conversion of 25-OHD to 1,25-OHD and 24,25-OHD. However, these authors mentioned that the mechanisms underlying the association between low serum 25-OHD levels and PHPT were not fully understood [29]. According to Clements et al [30] the half-life of 25-OHD may be shortened in PHPT due to an increase in hepatic inactivation. Clearly other factors may very well include the fact that there is a high incidence of vitamin D deficiency and insufficiency in the general population of the United States and in those with obesity [31]. As noted by Wermers et al [32], PHPT has been associated with increased body weight and BMI [33, 34]. The present study documents the existence of vitamin D deficiency or insufficiency in 73% of patients with PHPT. Thirty percent of patients had serum 25-OHD levels between 20 and 29 ng/mL, 37% of patients had serum 25-OHD levels between 10 and 19 ng/mL, and 6% of patients had levels less than 10 ng/mL. Some of the patients with normal 25-OHD levels had already been on vitamin D supplementation. Subnormal 25-OHD levels were present in 131 of 255 patients (51%) with normal BMI values, and in 95 of 141 patients (67%) with obesity.

PTH is the major stimulator of 1,25-OHD production in the kidney. Clarke [3] has indicated that in PHPT serum 1,25-OHD levels may be high normal or mildly increased with serum 25-OHD levels that are usually low normal, while Silverberg et al [21] have reported that serum 1,25-OHD levels are increased in 25% of patients with PHPT, while serum 25-OHD levels are in the lower end of the normal range. In the 334 patients who had 1,25-OHD measurements in this study, the mean level of 58 pg/mL and higher than normal levels were noted in 79 patients (24%).

The pathology of PHPT in this group of patients was in keeping with the generally acknowledged figure of 82% of patients having a benign adenoma and multiglandular disease in 15-20% of patients including hyperplasia of all four glands or multiple adenomas [9]. The adenomas as reported in the literature and as noted in this series have been more commonly located in the lower glands [35, 36]. Most of the adenomas consist of chief cells; but in the present group as reported in the literature there were several patients with functioning oxyphil cell adenomas. Parathyroid carcinoma remains a rare malignancy occurring in 0.5-2% of patients with PHPT [9]. Generally, such patients are 40 - 60 years of age with a similar sex predilection [9]. In the present series there were two males and two females with parathyroid carcinoma (2%) with ages of 32 to 60 years. Interestingly, despite the large size of these malignant lesions, serum calcium levels were mildly to moderately elevated ranging from 10.8 to 13 mg/dL.

Conclusions

This study which began 50 years ago indicates that PHPT continues to be a sporadic endocrine disorder especially in postmeno-

pausal females, and in most patients, it is characterized by hypercalcemia with increased or non-suppressed serum PTH levels and not related to the MEN1 disorder or familial isolated PHPT. Many patients had asymptomatic disease. They did not have osteitis fibrosa cystica, renal stone disease, or osteoporosis, but they did have a variety of non-traditional or non-classical disorders and related symptoms and complaints. Two percent of cases were related to parathyroid carcinoma. There is a continued incidence of approximately 20% of patients with calcium stone disease. In contrast to studies indicating that generally urolithiasis is seen in more males than females, there were two times as many females compared to males with calcium stone disease in the present series. The present study indicates no correlation of calcium stone disease with hypercalciuria since many patients with PHPT without stone disease had a comparable incidence of hypercalciuria. Twenty-six percent of patients had hypophosphatemia and 70% of our patients did have evidence of excess phosphorus excretion. In contrast to comments in the literature indicating that serum 25-OHD levels are normal in patients with PHPT, in the present series most patients had vitamin D deficiency or insufficiency. In keeping with DXA studies in PHPT, more patients tend to have the lowest bone mineral density (BMD) readings at the one-third radius site. In the present study of 300 patients who had DXA studies of spine, hip, and forearm, the lowest readings were evident at the one-third radius site in 59%; and of those patients with osteoporotic readings, the lowest readings were evident at the one-third site in 80 of 194 studies. Eighty-four percent of cases were due to a benign adenoma and 14% were due to multiglandular disease which included hyperplasia or benign adenomas. As a result of several international parathyroid conferences including the Fourth International Workshop held in 2013, parathyroid surgery is indicated for patients with classical or traditional PHPT [37]. In some patients with so-called non-traditional or non-classical disorders, there may be an indication for surgery related to the severity of symptoms. Clearly, parathyroid surgery is curative and may result in significant clinical improvement in some patients with non-traditional symptoms, while there are other patients who may continue with their symptom complex despite cure of the PHPT [21].

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Conflict of Interest

There are no potential conflict of interest or problems with copyrights of this manuscript.

Informed Consent

Informed consents for publication were obtained.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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