Analysis of 645 Patients with Primary Hyperparathyroidism with Special References to Cholelithiasis

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Abstract

Objective The clinical picture of primary hyperparathyroidism (PHPT) has changed during the past 50 years. It is currently unknown whether or not PHPT is associated with an increased risk of cholelithiasis.

Patients To determine the frequency of cholelithiasis in PHPT we analyzed 645 consecutive patients seen at Prague University Hospital from 1992 through 2002 and compared them with a normocalcaemic control group.

Methods We investigated 645 patients with proven PHPT (518 female and 127 males aged 20–80 years) during a period of 10 years. To determine the frequency of cholelithiasis in normal population we analyzed 2,015 patients receiving periodic health examination at an outpatient ward from January 1998 to December 1998 (1505 females and 510 males aged 24–85 years). A detailed history, physical examination, biochemical measurements and abdominal ultrasonography were done.

Results Cholelithiasis was proven in 157 of 518 women (30.3%) and in 11 of 127 men (8.66%) with PHPT. Their mean age was 59.67±12 years in women and 56.0±10 years in men. In the control group 260 of 1505 women (17.27%) and 54 of the 510 men (10.58%) had cholelithiasis. The mean age was 64.55±13.8 years in women and 61.2±12.4 in men. Only in the case of women, the difference was highly statistically significant (p<0.001). There were no significant differences between the mean values for the serum calcium level, bone alkaline phosphatase, total cholesterol, urinary hydroxyproline and body mass index in hyperparathyroid patients with and without cholelithiasis. However the hyperparathyroid women with cholelithiasis had an increased concentration of parathyroid hormone (236.1±56 pg/ml) compared with hyperparathyroid women without cholelithiasis (179.0±45 pg/ml), p<0.01.

Conclusion The mechanism of PTH associated gallstone formation may involve inhibition of gallbladder emptying, hepatic bile secretion and sphincter Oddi motility as well as modification of bile composition. While it might be difficult to prove it seems likely that the association of cholelithiasis with primary hyperparathyroidism in women with a high concentration of parathyroid hormone is more than merely coincidental and from our study it is obvious that a significant association exists.

Key words: primary hyperparathyroidism, parathormon, cholelithiasis

Introduction

The clinical picture of primary hyperparathyroidism (PHPT) has changed during the past 50 years. Earlier, PHPT was considered a rare illness characterized by bone disease and urinary calculi. Many new clinical features, such as hypertension, mental disturbances, myopathy, peptic ulcer disease, pancreatitis and cholelithiasis have been added to the clinical spectrum of PHPT (1, 2).

The development of gallstones in man has been ascribed to a variety of etiological factors and several diseases have been associated with an increased prevalence of gallstones. Clinical studies (3) and necropsy series (4, 5) have demonstrated that the prevalence of cholelithiasis increases with age and that it is higher in women than in men of any age.

It has been suggested that cholelithiasis is a common complication of primary hyperparathyroidism (6, 7). However there are papers which are at variance with those of other investigators who have reported that primary hyperparathyroidism is associated with an abnormally high frequency of gallstone disease (8).

To determine the frequency of cholelithiasis in primary hyperparathyroidism we analyzed 645 consecutive patients seen at Prague University Hospital from 1992 through 2002,
and compared these patients with a non-PHPT control group.

**Patients and Methods**

We investigated 645 patients with proven primary hyperparathyroidism (518 females and 127 males aged 20–80 years) during a period of 10 years. All had biochemically, surgically and histologically proven PHPT. The diagnosis of PHPT was confirmed by histopathological diagnosis based on a combination of different variables, including size and histological pattern of the excised glands. Off the 645 patients who underwent parathyroidectomy 602 had an adenoma and 43 hyperplasia. None of the 645 patients with PHPT had multiple endocrine neoplasia.

All 645 patients had a serum creatinine level of less than 100 μmol/l. No patient received any medical treatment known to affect bone or calcium metabolism. Serum calcium was measured by the method of Gitelman (9) with a normal range 2.25–2.65 mmol/l. The total activity of serum alkaline phosphatase and its bone isoenzyme was determined with 4-nitrophenyl phosphate as the substrate using a modified inactivation—inhibition method with a normal range for B-ALP 0.09–0.266 kat/l (10).

The urinary total hydroxyproline excretion was measured by the method described by Dubovský (11) with a normal range of 9.2–22.0 mmol/l creatine. All subjects were given a hydroxyproline free diet, for at least 48 hours prior to urine collection. In all patients the serum intact PTH was determined using immunoradiometric assay of intact PTH (means values 16–65 pg/ml) Nichols Institute, San Juan Capistrano, CA, USA. Serum total cholesterol was measured using automated analyzer after an overnight fast. The control subjects and patients with PHPT who had not undergone cholecystectomy were investigated by ultrasound scan explorations.

To determine the frequency of cholelithiasis in the normal population we analyzed 2015 patients receiving a periodic health examination at the outpatient ward in 3rd Medical Department of Prague Charles University Medical School from January 1998 to December 1998 (1,505 females and 510 males aged 24–85 years). A detailed history, physical examination, biochemical measurements and abdominal ultrasonography were done. Height and weight were measured.

Subjects were classified as having gallstones when the gallbladder lumen showed an acoustic shadow on ultrasound or if subjects had undergone cholecystectomy.

Statistical and discriminant analysis of the laboratory tests were performed by analysis of variance followed by the Duncans multiple range test (12). All mean values are presented with one standard deviation (SD). A p value of the 0.05 (two sided test) was accepted as the level of significance. The difference in percentages in both groups was tested using chi-square test. The results are highly significant for all diagnoses. The study protocol was approved by the ethics committee of the Charles University Hospital in Prague. Informed consent was obtained from all patients.

**Results**

A total of 645 cases of PHPT were diagnosed among
Czech residents between January 1992 and December 2002 (518 women and 127 men at 3rd Medical Hospital of Charles University of Prague. The patients with primary hyperparathyroidism had a significantly higher median level of PTH (207±68 pg/ml) and serum calcium (2.98±0.3 mmol/l) than the 2015 control patients (35±8 pg/ml, 2.42±0.2 mmol/l); (Table 1). Also significant differences were found in mean serum bone specific alkaline phosphatase and urinary hydroxyproline excretion between the group with hyperparathyroidism and the control group (p<0.01, Table 1).

At operation single adenoma formation was present in 602 patients, whereas diffuse hyperplasia was found in 43 other patients; 14 of the adenomas were found in an atypical anatomical localization. Kidney involvement due either to deposition of calcium in the renal parenchyma or to nephrolithiasis was present in 56.40% of our patients. The bone manifestation of hyperparathyroidism is hyperparathyroid osteodystrophy which occurred in 36.0% of our patients; (Table 2). The most common changes include resorption of the phalangeal tuft and replacement of the usually sharp cortical outline of the bone in the digits by an irregular outline (subperiosteal resorption).

The cohort of 645 patients was made up of the 124 premenopausal women and 394 postmenopausal women and 125 men with primary hyperparathyroidism. Cholelithiasis was proved in 168 patients with primary hyperparathyroidism (25.89%) of the entire group of 645 patients with PHPT. Of these 157 were women (of total 518 women, 30.3%) and 11 were men (of total 127 men, 8.66%). Their mean age was 59.67±12 years for women and 56.0±10 years for men (Table 3).

The elevated serum calcium level, bone alkaline phosphatase and urinary hydroxyproline in patients with cholelithiasis did not differ from those without cholelithiasis (Table 4). However our results showed increased concentrations of parathyroid hormone in women with cholelithiasis (236.1±56 pg/ml) compared with women without cholelithiasis (179.0+45 pg/ml) p<0.01. No such significant difference in concentration of parathyroid hormone was observed in men with and without cholelithiasis (Table 4).

In the control group 314 patients of the entire group of 2015 patients (15.6%) had cholelithiasis. There were 260 women of the entire group of 1505 women (17.27%) and 54 men of the entire group of 510 men (10.58%), (Table 3). Only in the case of women the difference was highly statistically significant (p<0.001). The mean age of control patients was 64.55±13.8 years for women and 61.2±12.4 years for men. We confirmed that the prevalence of cholelithiasis increases with age and that it is higher in women than in men of any age in both groups of patients (Table 5). In our control group as in the hyperparathyroid group the incidence of cholelithiasis peaks in the sixth decade.

Women with PHPT and cholelithiasis had a higher incidence of bone and kidney involvement; this was not found in men. From among 157 women with PHPT and cholelithiasis, 98 women had urolithiasis (62.4%) and 78 women had bone involvement (49.7%) which is higher in comparison with 361 women with PHPT without cholelithiasis, where 176 had urolithiasis (48.8%) and 114 had bone involvement (31.5%) (p<0.01).

In the case of men from among 11 men with PHPT and cholelithiasis, 4 men had urolithiasis (36.4%) and 3 men had bone involvement (27%) in comparison with 116 men without cholelithiasis where 50 men had urolithiasis (43%) and 37 men had bone involvement (31.8%). There was no significant difference between mean values for the serum total cholesterol, and body mass index in patients with PHPT with (6.76±1.52 mmol/l, 23.50±2.64 kg/m²) and without cholelithiasis (6.66±1.42 mmol/l, 24.10±3.07 kg/m²).
Discussion

In the present study 30.3% of the females and only 8.66% of the males with surgically verified PHP had gallstone disease. Women with hyperparathyroidism have a considerably greater incidence of cholelithiasis than men, because hyperparathyroidism is considerably more common in women. The prevalence of cholelithiasis in the observation groups statistically significantly different only in the case of women and did not differ in the case of men from that in the control group. Our results support the suggestion that cholelithiasis can be a clinical manifestation of PHP in the case of women. Our study covered patients with PHP of longer duration because 56% of our patients had nephrolithiasis or nephrocalcinosis and 36% had some kind of skeletal derangement.

Gallstone prevalence increases with age and gallstones are more prevalent in females of any age group as reported by Heaton (13). In patients with primary hyperparathyroidism cholelithiasis was found in 25–38% (7). An autopsy study of Sampliner correlated with clinical information suggested that approximately two thirds of the population with gallstones are asymptomatic (14). Methods most commonly used to determine gallstone prevalence include autopsy studies, determination of cholecystectomy rates and ultrasonography. A Danish screening ultrasound survey showed new gallstone formation in 3% of the population older than 40 years of age in each 5 year period (15). Gallstones are quite prevalent in most western countries. In the United States, autopsy series have shown gallstones in at least 20% of women and in 8% of men over the age of 40 (16).

Hepatic bile is a pigmented isotonic fluid with an electrolyte composition resembling blood plasma. The electrolyte composition of gallbladder bile differs from that hepatic bile because most of the inorganic anions, chloride and bicarbonate have been removed by reabsorption across the basement membrane. As a result of water reabsorption, the total concentration of calcium increases from 2.5 mmol/l in hepatic bile to 12 mmol/l in gallbladder bile.

Gallstones are crystalline structures formed by concentration or accretion of normal or abnormal bile constituents. These stones are divided into two major types: cholesterol gallstones usually contain more than 50% cholesterol monohydrate plus an mixture of calcium salts, bile acids and bile pigments, proteins, fatty acids and phospholipids. Pigment stones are composed primarily of calcium bilirubinate with varying amounts of cholesterol and protein. Biliary calcium is known to play an important role in the pathogenesis of gallstones. Calcium salts are present in all pigment gallstones and are also present in the core of most if not all cholesterol gallstones.

In studies by Layer et al (17) and Ahrendt (18) hypercalcemia decreases bile flow and increases biliary ionized calcium concentration in cats and prairie dogs. Similar effects of hypercalcemia on bile composition in humans might promote calcium salt precipitation in bile.

The clinical spectrum of primary hyperparathyroidism has undergone a continuous evolution since the classic description. There is still no definite explanation for the variability of the clinical manifestations of primary hyperparathyroidism. While it might be difficult to prove it seems likely that the association of cholelithiasis with primary hyperparathyroidism in women is more than coincidental and from our study it is obvious that significant association exists. In the present study, 30.3% of the females and only 8.66% of the males with surgically verified PHPT had cholelithiasis.

Although the pathogenesis of gallstones in PHPT remains unclear, several factors including hypercalcemia, high PTH level, impaired contractility of the gallbladder, changes in bile composition, genetic factors, estrogens and biliary tract infection may play important roles. Estrogens stimulate hepatic lipoprotein receptors, increase uptake of dietary cholesterol, increase biliary cholesterol secretion, inhibit synthesis of choenodeoxycholic acid and cause gallbladder hypomobility. All these could be reasons why men have less cholelithiasis (19).

PTH is an inhibitor of smooth muscle contraction in the cardiovascular system, in the gastrointestinal tract and other tissues such as trachea and uterus (20). The mechanism of PTH associated gallstone formation may involve inhibition of gallbladder emptying, hepatic bile secretion and sphincter Oddi motility as well as modification of bile composition. Gallbladder stasis may sequentially lead to an increased bile concentration, precipitation of cholesterol and calcium salts, retention of biliary precipitates and maturation of gallstones. In conclusion hyperparathyroidism should be considered whenever cholelithiasis occurs with unusual symptoms.

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References

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