Risk factors associated to kidney stones in primary hyperparathyroidism

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ABSTRACT. Nephrolithiasis is the most important clinical manifestation of primary hyperparathyroidism (PHPT), although nowadays this disorder is often asymptomatic. Clinical or biochemical differences between PHPT patients with and without nephrolithiasis have not been clearly identified in most of the previous studies. The aim of the study was to investigate clinical and biochemical parameters in kidney stone former (SF) and non-stone former (NSF) patients with PHPT in order to identify potential risk factors. Serum and plasma samples from 55 consecutive patients (43 females, 12 males) with PHPT were collected after overnight fasting; 24-h urine collection and a fresh sample of urine for sediment analysis were obtained from all patients. Clinical data were recorded in all. Out of 55 patients, 22 had kidney stones, which were symptomatic in 73%. SFs showed circulating PTH, total and ionized calcium, 1,25 dihydroxyvitamin D\textsubscript{3}, urinary calcium excretion and 24-h urine oxalate levels significantly higher than NSFs. Hypercalciuria was often concomitant with massive quantities of calcium oxalate crystals in urine sediment. Hypercalciuria and relatively high oxaluria were associated with stone formation with an odds ratio (OR) of 4.0 and 7.0, respectively, which rose to 33.5 when they coexisted. Hypomagnesuria and hypocitraturia were common in at least one third of all PHPT patients, but they were not associated to an increased OR. As expected, they were positively correlated with urine calcium excretion, suggesting that calcium, magnesium and citrate are commonly regulated at renal level. In conclusion, hypercalciuria, higher oxalate excretion and severe PHPT are associated with kidney stones in PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is associated with increased risk of renal stones. Like patients with other types of calcium nephrolithiasis, PHPT patients are usually asymptomatic during the initial phase of stone formation, while severe acute renal colics may occur when the disease progresses. The clinical presentation of PHPT has shifted towards milder or asymptomatic features and the proportion of patients with nephrolithiasis tends to decrease in more recent series (1-4). Significant differences in clinical or biochemical parameters between PHPT patients with and without nephrolithiasis have not been clearly identified in most of the previous studies (2, 5-8). Several metabolic features have been proposed to induce kidney stone formation in PHPT. In particular, hypercalciuria, encountered in 18-40% of PHPT patients (2, 6, 7), has been associated with nephrolithiasis (2, 3). Relatively low levels of urinary magnesium, which is known to inhibit calcium oxalate crystallization by complexing oxalate, are also a common finding in PHPT patients with nephrolithiasis (9, 10). Renal citrate excretion, a natural urinary inhibitor of calcium salt crystallization and crystal growth, has been reported to be reduced in PHPT patients with kidney stones (11). Less conclusive data are available on other potential factors promoting kidney stone formation, such as dietary oxalate, hyperuricosuria and urine proteins, which have been linked to calcium oxalate crystal formation (12-17).
The aim of the present study was to analyze several clinical and biochemical parameters in PHPT patients with and without nephrolithiasis, in order to identify clinical and biochemical background and risk factors for kidney stone development in PHPT.

**MATERIALS AND METHODS**

**Subjects**

We enrolled 55 consecutive patients [43 females and 12 males; median age at presentation 60 yr, interquartile range (IQR) 53-69 yr] referred to our Institute between May 2000 and December 2001 for diagnosis and management of PHPT. Informed consent was obtained from all patients. Diagnosis of PHPT was made based on high ionized calcium levels in the presence of elevated or inappropriately normal serum PTH levels (ionized calcium 1.48 mmol/l, IQR 1.43-1.58; total serum calcium 2.69 mmol/l, IQR 2.58-2.82; serum PTH 118 pg/ml, IQR 74-155). No PHPT patient belonged to families with familial benign hypercalcemic hypercalcaemia, as hypercalciuric patients did not show mutations in the DNA sequence analysis of the gene encoding the calcium sensing receptor. Thirty-three women out of 43 (77%) were in menopause, and 9 of them were being treated with hormone replacement therapy at the time of diagnosis. Hypertension was present in 62% (34 out of 55) of the patients. Anti-hypertensive therapy was modified in order to avoid administration of diuretics, with a wash-out period of at least one month.

**Laboratory tests**

Venous blood samples after an overnight fasting were obtained from all patients under a free diet for measurement of ionized calcium, total calcium, intact PTH, serum sodium and potassium, uric acid, glucose, creatinine, phosphatase, magnesium, alkaline phosphatase with bone isoenzyme, 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃. Plasma ionized calcium was measured by a potentiometric method (Radiometer ABL System 625, Copenhagen, Denmark) on heparinized blood samples within 30 min from blood collection (reference limits: 1.15-1.29 mmol/l). Serum intact PTH was measured by a chemiluminescent method (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA); 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ were measured by RIA kit (Immunodiagnostic Systems Limited, Boldon, UK). Calcium, phosphate, magnesium, sodium, potassium, uric acid, protein, glucose and creatinine were also measured in 24-h urine collections (from 07:00 h of the day before to 07:00 h of the examination day). Urine oxalate and citrate concentrations were measured by enzymatic commercial kits (Sigma Diagnostics, St. Louis, MO, USA, and Boehringer Mannheim GmbH, Biochemicals, Germany). Data obtained were checked at following controls. Fractional calcium excretion (FECa) was calculated as (UCa/UCr) x (SCR/SCa), where SCa is serum calcium in mg/dl, SCR is serum creatinine in mg/dl, UCa and UCr are urinary calcium and creatinine concentrations in mg/dl, respectively. A 2-h urine sample from the second urine of the morning was collected and prepared for microscope examination, as previously described (18). Crystals were examined by the same operator (F.G.B.) by a phase contrast microscope at 400x (high power field). Crystals were identified after their morphology and birefringence features and were semiquantitatively from 0 to ++++. Microscopic hematuria was defined as >1 red blood cell/field at 400x (19). All patients underwent an ultrasound (US) examination of the urinary tract and suspicious imaging for stones were confirmed by X-ray. All had bone mineral density evaluation by dual energy X-ray absorptiometry (DEXA) of the lumbar spine L2-L4 and of the proximal femur (femoral neck).

**Statistical analysis**

Several variables in the study were not normally distributed. Therefore, we reported medians and IQR throughout the manuscript. We used the Wilcoxon rank-sum test or the Fisher’s exact test for group comparisons of numerical and binary variables, respectively. We tested for linear correlation between variables by means of the Spearman rank correlation coefficient (r). We used Spearman’s statistics because robust to the influence of outliner observations. In addition, all correlation analyses were repeated excluding possible points of leverage. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional multiple logistic regression. The ORs were adjusted for plasma ionized calcium and PTH levels. We considered results significant if p-value was <0.05. All statistical tests were two-sided. We performed all analyses using the Stata statistical package (Stata Corporation, College Station, TX, USA; release 7.0).

**RESULTS**

**Clinical characteristics**

Nephrolithiasis, defined as a history of renal colics with stone expulsions and/or imaging identification or asymptomatic US imaging of stones, was identified in 22 patients (40%), that were defined as stone formers (SFs). Sixteen SFs (73%) reported 1 to 6 episodes of renal colic and 11 (59%) reported previous stone expulsion. Half of SFs needed removal of stones either by surgery (3 patients) or by lithotripsy (8 patients). Nephrocalcinosis (US hyperecogenicity of a renal papilla) was identified in one patient, who had a recurrence of hyperparathyroidism. Only 2 patients did not recall any symptom and were diagnosed with microcalcification by US imaging. Symptomatic stone disease (renal colic and stone expulsion) was recorded 13 yr (median; IQR 5-19 yr) before diagnosis of PHPT. No difference in age and sex distribution, frequency of estrogen deficiency and hypertension between SFs and non-stone formers (NSFs) was observed (Table 1). The median values of creatinine clearance were within the normal range in the two groups. Densitometry T-score, serum alkaline phosphatase levels and its specific bone isoenzyme were similar in SF and NSF patients.

**Biochemical characteristics of stone former and non-stone former patients**

**Severity of PHPT**

SF patients showed plasma ionized calcium, serum total calcium and PTH levels significantly higher than NSF patients, while serum phosphate and tubular maximal reabsorption of phosphate (TmP) were lower in SFs than NSFs (Table 2).