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ORIGINAL PAPER

Biochemical characterization of primary hyperparathyroidism with and without kidney stones

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Abstract The exact metabolic-physiological background for kidney stone formation in primary hyperparathyroidism (PHPT) is unclear. To obtain clarification, this retrospective data analysis was conducted in 131 patients with PHPT who had undergone a detailed ambulatory evaluation on a random diet since 1980. The baseline biochemical presentation of 78 patients with PHPT with stones was compared with that of 53 patients without stones. Compared to those without stones, the stone-forming patients had a more marked hypercalciuria (343 ± 148 vs. 273 ± 148 mg/day, $P < 0.01$). Urinary saturation of calcium oxalate and brushite was significantly higher in stone-formers. Serum PTH and fasting urinary calcium were similar between the two groups, but serum phosphorus was significantly lower in stone-formers. Serum calcitriol (available in some patients) showed a slightly higher mean value in stone-formers but the difference was not significant. The increment in urinary calcium after oral load of 1-g calcium was twofold higher among stone-formers. Radial shaft and L2–L4 bone mineral densities resided within the normal ranges. Stone-formers with PHPT display exaggerated urinary calcium excretion due to intestinal hyperabsorption of calcium, contributing to a greater enhancement of the saturation of stone-forming calcium salts.

Keywords Primary hyperparathyroidism · Nephrolithiasis · Calcium absorption · Hypercalciuria

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Introduction

Nephrolithiasis is a common complication of primary hyperparathyroidism (PHPT). Though decreasing in incidence, kidney stones still occur in 15–20% patients with this condition.

The cause for kidney stone formation among patients with PHPT is unknown. Before early detection was made possible by routine analysis of serum calcium, nephrolithiasis and clinical bone disease were the two major complications of PHPT. It has been postulated that nephrolithiasis and bone disease resulted from different pathogenetic backgrounds, owing to varying calcium intakes [1]; structural differences in parathyroid hormone elaborated by abnormal parathyroid tissue [2]; and different haplotypes of calcium-sensing receptors [3].

In 1975, Peacock et al. [4] divided patients with PHPT according to the degree of intestinal calcium absorption, and reported that patients with stones clustered into the group with high intestinal calcium absorption while those without stones segregated into the group with normal calcium absorption. In 1980, Broadus et al. [5] confirmed this finding of the association of stones with increased intestinal absorption of calcium, and showed that the stimulation of 1,25-$(OH)_2$ vitamin D synthesis was responsible for the high calcium absorption. In 1981, we found that patients with PHPT presenting with stones could not be distinguished from those without stones either in their biochemical picture or in urinary saturation of stone-forming salts [6]. However, the study by Patron et al. [7] published in 1987 concurred with the earlier findings and showed that stone-formers have an exaggerated calciuric response to calcium load and had significantly higher serum calcitriol concentration compared to the non-stone-formers. In 1990, Silverberg et al. [8] found that urinary calcium of patients with stones was significantly

higher than of those without stones, when expressed as total daily output but not when it was expressed relative to urinary creatinine. Our detailed literature review since 1977 disclosed conflicting reports on the biochemical–physicochemical distinction between stone-forming and non-stone-forming variants of PHPT [4–13].

Since our publication in 1980, we have performed detailed evaluation of 78 patients with stones and 53 without stones suffering from PHPT. This retrospective data analysis was undertaken to reexamine the biochemical differences between stone-formers with PHPT and those without stones. Our goal was to ascertain whether urinary calcium is higher in stone-formers compared with non-stone-formers, and if so, to determine its cause and role in stone formation.

Methods

Patient data

Data were retrieved from 131 patients who were evaluated for PHPT in an outpatient setting by the mineral metabolism group of the University of Texas Southwestern Medical Center since 1980. They satisfied the following criteria: (a) ≥18 years of age of either gender or ethnicity, (b) biochemical evidence of PHPT, shown by hypercalcemia with high or inappropriately high serum PTH without secondary causes of parathyroid stimulation, (c) availability of fasting urinary calcium and 4-h urinary calcium following oral load of 1-g calcium [14, 15], (d) measurement for urinary stone risk factors in one or two 24-h urine collections on random diet [16, 17], and (e) adequacy of 24-h urine collection, indicated by urinary creatinine ±30% of idealized urinary creatinine (22.1 mg/kg in men, 17.2 mg/kg creatinine in women) [18]. Exclusion criteria were: (a) moderate–severe chronic diarrheal syndrome (due to ileal resection, bypass surgery, Crohn's disease, or fat malabsorption) and (b) impaired renal function (endogenous creatinine clearance <70 mL/min). None of the patients had radiological evidence of osteitis fibrosa.

Of the 131 patients, 78 had stones and 53 patients were without stones. Fifty-six (38 with stones and 18 without stones) underwent parathyroid exploration with removal of abnormal parathyroid tissue at our institution, after undergoing the diagnostic evaluation. The surgery was performed by an experienced team led by Dr William Snyder of the Department of Surgery at UT Southwestern. The histological classification of excised tissue was obtained from the pathology report.

The formation of kidney stones was confirmed by passage or removal of stones, or by presence of radioopaque mass in the kidney or ureter on roentgenogram. Available stones were analyzed and showed the presence of calcium oxalate and/or calcium phosphate. From each patient, fasting serum was analyzed for calcium, phosphorus, alkaline phosphatase, immunoreactive parathyroid hormone (iPTH), 25-hydroxyvitamin D (25-OHD) and 1,25-dihydroxyvitamin D (calcitriol) and creatinine. The assay for 25-OHD and calcitriol was inadvertently omitted in some patients. In all patients, 24-h urine samples were obtained for stone risk factors, which included calcium, phosphorus, oxalate, pH, citrate, ammonium, sulfate, uric acid, sodium, potassium, creatinine and total volume.

All patients underwent the "fast and calcium load test" [14, 15]. After collecting a 2-h urine sample (fasting) after an overnight fast, a 4-h urine sample (post-load) was collected after oral ingestion of 1-g calcium mixed in synthetic meal. Bone mineral density (BMD) was obtained in the distal third of the radius in 73 stone-formers and 52 non-stone-formers, and in the L2–L4 vertebrae in 40 stone-formers and 38 non-stone-formers.

Analytical methods

Serum calcium, phosphorus, alkaline phosphatase and creatinine were determined in an autoanalyzer (SYNCHRON CX9 ALX system, Beckman Coulter, Inc., Fullerton, CA). Serum 25-OHD and calcitriol were measured by ELISA (ALPCO Diagnostics, Windham, NH). During the course of the study, several immunoassays for PTH were utilized with different but well-defined upper normal limits. The results were expressed as the percentage of respective upper normal limits. Urinary stone risk factors were analyzed by methods previously described [16, 17]. From these tests, relative saturation ratio (RSR) of calcium oxalate and brushite ($CaHPO_4{\cdot}2H_2O$) was calculated by using the Equil 2 computer program [19], Endogenous creatinine clearance was calculated from 24-h urinary creatinine and corresponding serum creatinine. The difference between post-load and fasting calcium (increment in urinary calcium) gave an indirect measure of intestinal calcium absorption [14]. Fasting urinary calcium and BMD gave measures of bone loss. Radial shaft BMD was measured by single photon absorptiometry (Norland Instruments, Fort Atkinson, WI) [20] or by dual energy X-ray absorptiometery (DEXA) (Hologic, Waltham, MA). L2–L4 BMD was obtained by DEXA (Hologic or Lunar, Madison, WI). Results were presented as Z scores in order to correct for methodological differences.

Statistical analysis

The 2-sample t test was used to compare the data between the two groups. For skewed data, log transformation was performed before analysis. Fisher's exact test was used to

assess the significant difference in the percentage of patients between the two groups. The data were analyzed by using SAS 9.1 (SAS Institute, Cary, North Carolina). Results were expressed as mean ± SD.

Results

Baseline presentation

The majority of patients were women among both stone-formers and non-stone-formers (Table 1). A larger percentage of stone-formers were men (38 vs. 19%). Stone-formers were significantly younger than non-stone-formers. At parathyroid exploration, a single glandular involvement with adenoma was encountered in 84% of patients with stones and 83% of those without stones.

Serum calcium concentration was high in both groups and not significantly different from each other (Table 1, reference range 8.5–10.6 mg/dL). Serum phosphorus concentration was low normal in both groups; it was significantly lower in the stone-formers than non-stone-formers (Table 1, reference range 2.5–4.5 mg/dL). Serum PTH was high in both groups without a significant difference between the two groups. Both groups had normal serum alkaline phosphatase, 25-OHD, and endogenous creatinine clearance; these tests did not differ significantly between the two groups.

Urinary biochemistry and physicochemistry

Urinary calcium was high in both groups; it was significantly higher in the stone-formers compared with non-stone-formers (Table 2; Fig. 1, upper normal limit on a random diet is 250 mg/day). There was no significant difference in urinary phosphorus, oxalate, pH, ammonium, sulfate, uric acid, sodium, or potassium between the two groups. Urinary citrate and total volume tended to be lower in stone-formers compared to non-stone formers, but the difference did not reach significance. The RSR of calcium oxalate was significantly higher in stone-formers than in non-stone formers by 35%; that of brushite was also significantly increased in stone-formers by 43%.

Other tests

Fasting urinary calcium was high in both groups; it did not differ significantly between the two groups (Table 3). The majority of patients from both the groups had high values (Fig. 2, upper normal limit 0.11 mg/dL glomerular filtrate). The mean values of *Z* scores of radial shaft and L2–L4 BMD were lower in stone-formers compared with non-stone-formers; the difference was significant for radial shaft BMD.

The increment in urinary calcium post-calcium load was about twofold higher in the stone-formers than in those without stones (Table 1; Fig. 1, mean normal 0.125 mg/dL GF from Broadus et al. [14]). The serum calcitriol (available in only some patients) tended to be higher in stone-formers compared to non-stone-formers, but the difference was not significant (Table 1).

Discussion

This retrospective data analysis was conducted in an effort to identify metabolic-physiological disturbances differenti-

Table 1 Demography and baseline presentation

	Stone-formers	Non-stone formers	*P*
Number of patients	78	53	
Gender, M/F	30/78	10/43	<0.05
Age, years	49.8 ± 13.5	53.8 ± 13.4	<0.05
Serum calcium, mg/dL	10.8 ± 0.7	10.8 ± 0.7	NS
Phosphorous, mg/dL	2.55 ± 0.43	2.74 ± 0.53	<0.05
Alkaline phosphatase, U/L	97 ± 61	89 ± 45	NS
PTH, % upper limit of normal	183 ± 236	167 ± 84	NS
25-OH vitamin D, ng/mL	20.9 ± 10.7 (31)	23.8 ± 15.4 (23)	NS
Calcitriol, pg/mL	56.7 ± 24.6 (31)	51.7 ± 21.3 (23)	NS
Endogenous creatinine clearance, mL/min	101 ± 29	96 ± 36	NS
Parathyroid surgery			
No. of patients	38	18	NS
Adenoma, % patients	84	89	NS
Single, % patients	84	83	NS

Numbers in parenthesis indicate number of patients

M Male; *F* female; *PTH* parathyroid hormone; *NS* not significant

Table 2 Urinary biochemistry and physicochemistry

	Stone-formers	Non-stone -formers	*P*
Urinary calcium, mg/day	341 ± 147	274 ± 137	<0.01
Phosphorous, mg/day	871 ± 294	807 ± 321	NS
Oxalate, mg/day	32.3 ± 12.7	28.8 ± 9.0	NS
pH	6.12 ± 0.36	6.07 ± 0.52	NS
Citrate, mg/day	593 ± 323	654 ± 396	NS
Ammonium, mEq/day	30.2 ± 17.8	27.4 ± 9.1	NS
Sulfate, mmol/day	18.1 ± 7.7	16.9 ± 7.9	NS
Uric acid, mg/day	545 ± 207	500 ± 201	NS
Sodium, mEq/day	161 ± 59	155 ± 85	NS
Potassium, mEq/day	50.2 ± 19.7	53.9 ± 28.0	NS
Total volume, L/day	1.92 ± 0.93	2.16 ± 0.78	NS
Relative saturation ratio			
Calcium oxalate	9.37 ± 4.14	6.92 ± 4.53	<0.01
Brushite	3.30 ± 1.90	2.30 ± 2.62	<0.001

NS Not significant

ating stone-forming patients with PHPT from those without stones. Serum calcium, PTH and fasting urinary calcium were equally elevated in stone-formers and non-stone-formers. However, the hypercalciuria was more marked and intestinal calcium absorption (from the calciuric response to oral calcium load) was significantly higher in stone-formers than in non-stone-formers. Urinary saturation of stone-forming calcium salts was greater in stone-formers than in non-stone-formers.

This study provides some elucidation of the physicochemical background for stone formation in PHPT. We were unable to confirm earlier reports of urinary citrate being significantly lower among stone-formers compared with non-stone-formers [10, 21]. Our findings support the conclusion of Peacock et al. [4], Broadus et al. [5] and Patron et al. [7] that hypercalciuria of intestinal origin is pathogenetically important in stone formation. Hypercalciuria may enhance urinary saturation of stone-forming salts, as shown here by a significant increase in urinary saturation of calcium oxalate and brushite in stone-formers compared with non-stone-formers, a finding not shown by others [4–6]. Urinary calcium may also bind urinary inhibitors, accounting for reported reduction in inhibitor activity against calcium oxalate crystallization among stone-forming patients with PHPT [22].

A review of the literature during the past three decades disclosed considerable disagreement in the biochemical presentation of PHPT between stone-formers and non-stone-formers. While hypercalciuria was invariably reported, it was shown to be more marked in stone-formers compared to non-stone-formers in five studies [4, 5, 8, 10, 11], the same in two studies [6, 13], and less marked in one study [9]. In the two studies conducted elsewhere in the 1970s [4, 5], the patients with PHPT were divided into two groups according to high or normal intestinal calcium absorption. The majority of patients with high calcium absorption suffered from kidney stones, whereas a minority of patients with normal calcium absorption had stones. In our earlier study [6] reporting on patients evaluated before 1980, we divided the patients into two groups depending on whether or not they had stones. We found no clear difference in urinary calcium or intestinal calcium absorption between the two groups. In the current study of patients with PHPT evaluated since 1980, our findings of exaggerated intestinal absorption and urinary excretion of calcium among stone-formers were in accord with earlier reports from elsewhere [4, 5, 7] but not with our earlier report [6]. We have no clear explanation for this discrepancy, except to suggest that the severity of PHPT may have varied between the two reports. Before 1980, many patients with moderate–severe PHPT were referred to the mineral metabolism group by practicing physicians. Since then, the referral of patients to our clinics has declined due to easier identification of PHPT being made possible by the introduction of commercial PTH assays and bone densitometry.

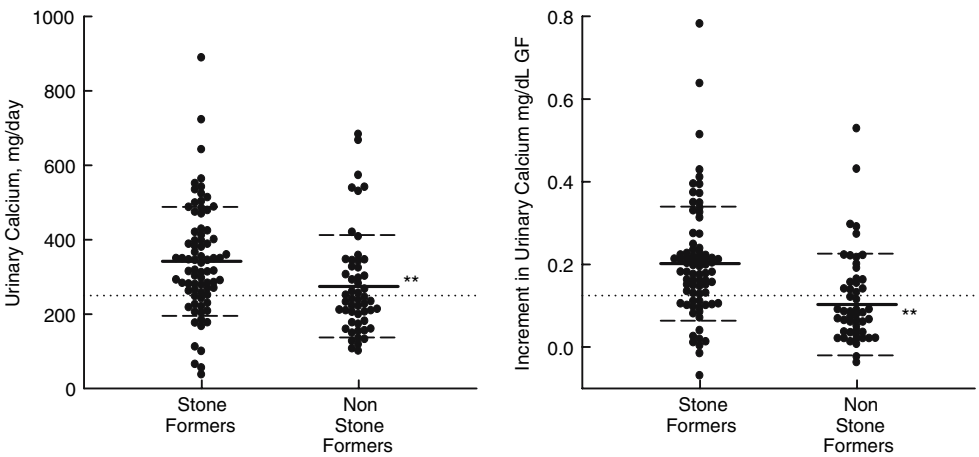

Fig. 1 Twenty-four hour urinary calcium and increment in urinary calcium after oral calcium load. The *dashed horizontal line* indicates upper normal limit of urinary calcium (*left panel*) and mean normal value of increment in urinary calcium (*right panel*)

Table 3 Other tests

	Stone-formers	Non-stone-formers	*P*
Fasting urinary Ca, mg/dL GF	0.134 ± 0.067	0.137 ± 0.095	NS
Post-load urinary Ca, mg/dL GF	0.335 ± 0.167	0.241 ± 0.123	<0.001
Increment in urinary Ca, mg/dL GF	0.202 ± 0.138	0.103 ± 0.123	<0.01
Radial shaft BMD *Z* score %	93.3 ± 14.5	98.5 ± 14.2	<0.05
L2–L4 BMD *Z* score %	93.3 ± 15.9 (40)	97.3 ± 18.6 (38)	NS

Ca calcium; *dL* deciliter; *GF* glomerular filtrate; *BMD* bone mineral density

The typical patients have increasingly become those with milder disease identified from within the medical center complex. In support of this explanation, the earlier study [6, 21] disclosed a more marked depression of radial shaft BMD, and a more prominent hypercalciuria among stone-formers, compared to the current study.

Fasting urinary calcium was moderately elevated to a similar degree in the two groups, whereas the calciuric response to an oral calcium load was exaggerated only in stone-formers. Thus, hypercalciuria of non-stone-formers may have been primarily skeletal in origin, whereas the more marked hypercalciuria of stone-formers probably originated from both increased bone loss and high intestinal calcium absorption.

Both Broadus et al. [5] and Patron et al. [7] concluded that a stimulated synthesis of calcitriol was responsible for the increased calcium absorption among stone-formers. Unfortunately, we were able to measure serum calcitriol in only 40% of patients. The cause for the increased calcitriol synthesis in stone-formers, if it exists, remains obscure. It appears to be not related to varying secretion of PTH, since serum concentration of PTH was equally elevated in stone-formers and non-stone-formers as previously reported [5–10, 12]. Patron et al. [7] suggested that higher renal mass might be responsible for the higher calcitriol synthesis in stone-formers. The authors showed that circulating calcitriol correlated significantly to both the creatinine clearance and age and concluded that young patients with high renal mass would have higher production of calcitriol for the same degree of PTH hypersecretion. We were not able to demonstrate the same relationships in this retrospective study.

In the present study, we found serum phosphorus concentration to be low normal in both groups, with a greater depression among stone-formers. Our data suggest that hypophosphatemia may have had a role in stimulating calcitriol synthesis, contributing to the increased intestinal calcium absorption among stone-formers with PHPT.

From previous results, we suggest the following scheme for the development of exaggerated hypercalciuria in stone-formers: equivalent stimulation of PTH secretion → renal phosphate leak → more prominent decline in serum P → stimulation of calcitriol synthesis → intestinal hyperabsorption of calcium → exaggerated hypercalciuria. This scheme is only implied by our data, since our study was a retrospective data analysis that was not originally designed to test the validity of this scheme.

Prior reports have suggested that bone loss may be more marked among patients without stones [4]. We were unable to confirm this finding. Fasting urinary calcium was only modestly increased and did not differ between stone-formers and non-stone-formers. BMD of radial shaft in stone-formers was only slightly depressed from normal subjects matched for age and gender, and was lower than in non-stone-formers. No one in this study had osteitis fibrosa. The findings disclosed here, in contradiction to our earlier report [6], may reflect evolving presentation of PHPT with milder form of the disease.

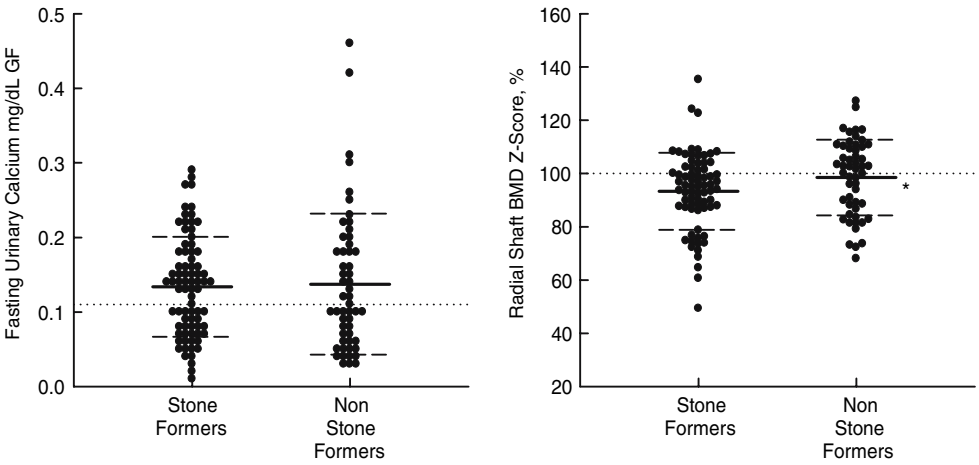

Fig. 2 Fasting urinary calcium and L2–L4 bone mineral density. The *dashed horizontal line* depicts the upper normal limit for fasting urinary calcium in the *left panel*, and the 100 percentile value (representing the mean age-matched value for each subject) in the *right panel*

This study has obvious limitations. As a retrospective data analysis, it lacked an original hypothesis. Moreover, the majority of patients had kidney stones, probably reflecting the interest of our mineral metabolism group in nephrolithiasis research. A more meaningful statistical assessment of potentially meaningful relationships was precluded by a limited number of patients and the failure to measure critical tests in all patients.

In conclusion, stone-formers with PHPT have more severe hypercalciuria due to intestinal hyperabsorption of calcium, contributing to a greater enhancement of urinary saturation of stone-forming calcium salts. The possible role of renal phosphate leak, suggested by this retrospective data analysis, deserves further exploration.

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