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Role of 1,25-Dihydroxy Vitamin D_3 and Parathyroid Hormone in Urinary Calcium Excretion in Calcium Stone Formers

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Purpose: To find out the possible role of $1,25(OH)_2$ vitamin D_3 [$1,25(OH)_2D_3$] and parathyroid hormone (PTH) as intrinsic factors in urinary calcium stone formers (SFs), we investigated their relationship with serum and urinary biochemical parameters. **Materials and Methods:** A total of 326 calcium SFs (male: 204, female: 122) were enrolled and underwent outpatient metabolic evaluations including $1,25(OH)_2D_3$ and PTH as well as serum and 24-hour urinary biochemical parameters. As control, 163 age- and sex-matched (2:1) individuals (non-SFs) who have never urinary stone episode were included. **Results:** $1,25(OH)_2D_3$ level was positively correlated with urinary calcium excretion ($r=0.347$, $p<0.001$). The hypercalciuric group and recurrent SFs had higher serum $1,25(OH)_2D_3$ levels than the normocalciuric group ($p<0.001$) and first SFs ($p=0.050$). In the adjusted multiple linear regression analysis, serum $1,25(OH)_2D_3$ level ($\beta=0.259$, $p<0.001$) and serum PTH level ($\beta=-0.160$, $p<0.001$) were significantly correlated with urinary calcium excretion. The patients in highest tertile of $1,25(OH)_2D_3$ had a more than 3.1 fold risk of hypercalciuria than those in the lowest tertile (odds ratio=3.14, 95% confidence interval: 1.431–6.888, $p=0.004$). No correlation was observed between PTH and $1,25(OH)_2D_3$ ($R=0.005$, $p=0.929$) in calcium SFs, while a negative correlation was found in controls ($R=-0.269$, $p=0.001$). **Conclusion:** $1,25(OH)_2D_3$ was closely correlated with urinary calcium excretion, and high $1,25(OH)_2D_3$ levels were detected in the hypercalciuric group and in recurrent SFs. However, $1,25(OH)_2D_3$ was not correlated with PTH in calcium SFs. These findings suggest that $1,25(OH)_2D_3$ might be important intrinsic factor for altered calcium regulation in SFs.

Key Words: 1,25-dihydroxy-vitamin D_3, calcium, parathyroid hormone, urolithiasis

INTRODUCTION

The incidence of urinary stone formation has been increasing recently, and the lifetime risk of stone formation is estimated at 5–12% in Europe and the USA.[1-3] Envi-

ronmental, genetic, nutritional, intrinsic, anatomic and metabolic factors contribute to urinary stone formation.[4-8] Hypercalciuria, regardless of its underlying mechanism, is the most common metabolic abnormality in patients with calcium stones.[9,10] Calciuria is a net loss of calcium in the urine after renal reabsorption and the final result of numerous regulatory processes.[11] Parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2D_3$] are considered to be the endocrine regulators of calcium homeostasis. PTH secretion, which is triggered by hypocalcemia, increases extracellular calcium levels by stimulating bone resorption, renal reabsorption, and intestinal calcium absorption indirectly through the synthesis of $1,25(OH)_2D_3$ in the kidney.[12] Due to their role in the control of calcium levels, PTH and $1,25(OH)_2D_3$ have received much attention. However, the exact roles of these intrinsic factors in urolithiasis remain to be elucidated. The aim of this study was to find the association between PTH or $1,25(OH)_2D_3$ and serum and urinary metabolites and the correlation between PTH or $1,25(OH)_2D_3$ and urinary calcium excretion in calcium stone formers (SFs).

MATERIALS AND METHODS

Patients

Between 2009 and 2011, 326 calcium SFs (male: 204, female: 122) with informed consent agreement were enrolled. Pediatric patients (<16 years) and patients with incomplete 24 hour urine collection, impaired renal function (serum creatinine >1.5 mg/dL), infection stones, radiolucent stones, malformation of the urological system, hypercalcemia, prior bowel surgery, or a prior diagnosis of primary hyperparathyroidism or other systemic diseases (any cancer, alcoholic liver disease and osteoporosis drug medication like calcium pills etc.), that might affect calcium and bone metabolism were excluded. Controls were selected with similar age and gender proportions to the calcium SFs, and subjects were screened to ensure that they were within the normal range of all laboratory findings and had no history of urinary stone. The Ethics Committee of our institution approved this protocol. The collection and analysis of all samples was approved by the Institutional Review Board of our institution. The data collected included the history of kidney stones and medications, and a metabolic evaluation such as 24-hour urinary and fasting serum biochemistry as well as intact PTH and $1,25(OH)_2D_3$ which was performed at the same time. Intact PTH was measured with an immunoradiometric assay with an ELSA-PTH kit (CIS Bio International, Paris, France), and $1,25(OH)_2D_3$ levels were also measured with a radioimmunoassay with a $1,25(OH)_2D_3$ RIA kit (Immunodiagnostic Systems Ltd., Boldon Colliery, Tyne & Wear, UK). The metabolic evaluation was performed at least 4–6 weeks after returning to their normal life. SFs were advised to continue their usual diet, and none were placed on a low calcium diet or preventive medications. Patients were divided into two groups according to urinary calcium excretion (hypercalciuria vs. normocalciuria) and the prior stone episode (first time vs. recurrent), respectively, and the clinical and laboratory characteristics of each group were compared. Hypercalciuria was defined as 24 h urinary calcium excretion of more than 300 mg per 24 hour in men and 250 mg per 24 hour in women. Hypercalciuric SFs and normocalciuric SFs were 19.9% (65/326) and 80.1% (261/326), while the fractions of first SFs and recurrent SFs were 57.1% and 42.9%, respectively (total 324 patents were analyzed due to 2 missing values). To compare $1,25(OH)_2D_3$ and PTH levels between calcium SFs and controls, 163 age- and sex-matched controls were included.

Data analysis

Clinical characteristics, serum laboratory parameters including PTH and $1,25(OH)_2D_3$, and urinary biochemical parameters were compared in each group. The correlation between PTH or $1,25(OH)_2D_3$ and serum and urinary parameters was assessed by the Spearman correlation test. The relationship between PTH and $1,25(OH)_2D_3$ in calcium SFs and controls was assessed by the linear regression test. The differences in serum and urinary metabolites between subgroups were assessed by the Student's t-test. Multiple linear regression analysis was performed to evaluate the association between 24 h urinary calcium excretion and serum $1,25(OH)_2D_3$ or PTH after adjusting for the effects of other parameters. The logistic regression was carried out to identify the association between hypercalciuria and tertiles of serum $1,25(OH)_2D_3$. Dependent variable was the hypercalciuria; independent variable was tertile of serum $1,25(OH)_2D_3$. Tertile cut-off points were determined on variable distribution of patients in the full study group. Odds ratios (ORs) and 95% confidential intervals (CIs) were estimated using logistic regression models. Statistical analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Clinical and laboratory parameters for the study populations

The mean age of the study population was 45.8±12.3 years and the mean body mass index (BMI) was 24.5±3.4 kg/m^2. The mean serum calcium, phosphate, uric acid, PTH, and 1,25(OH)$_2$D$_3$ were 9.49±0.49 mg/dL, 3.61±0.62 mg/dL, 5.65±1.52 mg/dL, 28.0±14.4 pg/mL, and 52.5±19.0 ng/mL, respectively.

Relationship between 1,25(OH)$_2$D$_3$ or PTH and clinico-laboratory parameters

1,25(OH)$_2$D$_3$ levels were positively correlated with 24 h urinary phosphate (r=0.120, p=0.030), uric acid (r=0.158, p=0.004), pH (r=0.170, p=0.002), and calcium excretion (r=0.347, p<0.001). However, in the multiple linear regression analysis, the 1,25(OH)$_2$D$_3$ level was correlated significantly only with 24 h urine calcium excretion (β=0.355, p<0.001).

PTH was positively correlated with age (r=0.146, p=0.008) and sex (r=0.148, p=0.008), but inversely correlated with 24 h urinary magnesium (r=-0.116, p=0.036) and calcium excretion (r=-0.193, p<0.001). In the multiple linear regression analysis, PTH level was inversely correlated with 24 h urinary calcium excretion (β=-0.188, p<0.001) (Table 1).

Comparison of clinical characteristics and serum parameters according to calciuria and stone episodes

There were no significant differences in parameters such as age, serum calcium, phosphate and uric acid between the hypercalciuria group and the normocalciuria group, or between first SFs and recurrent SFs. The serum 1,25(OH)$_2$D$_3$ level was significantly higher in the hypercalciuric group and recurrent SFs than in the normocalciuric group and first SFs (p<0.001, p=0.050, respectively). However, there were no significant differences in PTH levels between these groups (p=0.295, 0.256, respectively) (Table 2).

Univariate and multivariate analysis for the relationship between urinary calcium excretion and other parameters

Urinary calcium excretion was positively correlated with BMI (r=0.149, p=0.007), stone episodes (r=0.151, p=0.006), 1,25(OH)$_2$D$_3$ level (r=0.347, p<0.001), 24 h urine total vol-

Table 1. Relationships between Serum 1,25(OH)$_2$D$_3$ or PTH Levels and Clinical and Laboratory Parameters

	Serum 1,25(OH)$_2$D$_3$				Serum PTH			
	Spearman correlation		Linear regression		Spearman correlation		Linear regression	
	R	p value	β	p value	R	p value	β	p value
Age	-0.026	0.643			0.146	0.008	0.088	0.117
Sex (male/female)	-0.025	0.652			0.148	0.008	0.102	0.068
BMI	0.015	0.789			0.028	0.614		
Family history	0.048	0.391			0.008	0.893		
Stone episode	0.108	0.051			-0.019	0.735		
Serum								
Sodium	-0.005	0.928			0.107	0.054		
Calcium	0.069	0.212			-0.067	0.226		
Phosphate	-0.057	0.303			-0.012	0.834		
Uric acid	-0.067	0.228			0.019	0.730		
PTH/1,25(OH)$_2$D$_3$	-0.021	0.710			-0.021	0.710		
24 hrs urine								
Total volume	0.035	0.529			-0.059	0.292		
Sodium	0.069	0.217			0.040	0.470		
Calcium	0.347	<0.001	0.355	<0.001	-0.193	<0.001	-0.188	<0.001
Phosphate	0.120	0.030	-0.081	0.256	-0.085	0.126		
Magnesium	-0.072	0.197			-0.116	0.036	-0.038	0.494
Citrate	-0.024	0.667			-0.053	0.339		
Oxalate	-0.081	0.144			0.031	0.577		
Uric acid	0.158	0.004	-0.003	0.971	-0.062	0.261		
pH	0.170	0.002	0.101	0.062	-0.095	0.087		

1,25(OH)$_2$D$_3$, 1,25-dihydroxy vitamin D$_3$; PTH, parathyroid hormone; BMI, body mass index; pH, potential of hydrogen.

Table 2. Comparison of Clinical Characteristics and Serum Parameters According to Calciuria and Stone Episodes

	According to calciuria			According to stone episodes		
	NC (n=274)	HC (n=52)	*p* value	FSF (n=185)	RSF (n=139)	*p* value
No. gender (%)			0.044			0.109
M	178 (65.0)	26 (50.0)		109 (58.9)	94 (67.6)	
F	96 (35.0)	26 (50.0)		76 (41.1)	45 (32.4)	
Age (yrs)	45.4±12.5	47.9±10.9	0.176	45.4±13.0	46.3±11.5	0.527
Body height (cm)	164.6±8.2	163.2±9.9	0.282	163.9±8.6	164.9±8.3	0.297
Body weight (kg)	65.6±10.8	69.4±13.0	0.022	65.1±11.5	67.7±10.8	0.041
BMI (kg/m^2)	24.2±3.3	26.0±3.8	<0.001	24.2±3.6	24.8±3.1	0.096
Serum						
Creatinine	1.01±0.21	0.93±0.16	0.007	1.00±0.21	1.01±0.20	0.623
Calcium (mg/dL)	9.46±0.49	9.60±0.49	0.058	9.45±0.52	9.53±0.44	0.151
Phosphate (mg/dL)	3.60±0.60	3.63±0.74	0.798	3.65±0.64	3.56±0.60	0.183
Uric acid (mg/dL)	5.70±1.50	5.39±1.57	0.174	5.61±1.56	5.70±1.47	0.605
PTH (pg/mL)	28.3±14.7	26.1±12.2	0.295	28.7±16.1	26.9±11.6	0.256
$1,25(OH)_2D_3$ (ng/mL)	50.8±17.9	61.3±21.9	<0.001	50.7±17.8	54.8±20.3	0.050

NC, normocalciuria; HC, hypercalciuria; FSF, first stone former; RSF, recurrent stone former; No, number; M, male; F, female; BMI, body mass index; PTH, parathyroid hormone; $1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3.

ume (r=0.305, p<0.001), urinary sodium (r=0.502, p<0.001), phosphate (r=0.469, p<0.001), magnesium (r=0.375, p<0.001), citrate (r=0.277, p<0.001), uric acid excretion (r=0.553, p<0.001), and pH (r=0.170, p=0.002), but was inversely correlated with serum PTH level (r=-0.193, p<0.001). To evaluate the association between 24 h urinary calcium excretion and serum vitamin D_3 or PTH after adjusting for the effects of other parameters, multiple linear regression analysis was performed using parameters correlated with urinary calcium excretion in Pearson correlation. Stone episodes (β=0.083, p=0.045), serum $1,25(OH)_2D_3$ (β=0.259, p<0.001) and PTH (β=-0.160, p<0.001) levels, and urinary sodium (β=0.270, p<0.001), phosphate (β=0.192, p<0.001) and uric acid (β=0.243, p<0.001) levels, were significantly associated with calcium excretion (Table 3). The patients in highest tertile of $1,25(OH)_2D_3$ had a more than 3.1 fold risk of hypercalciuria than those in the lowest tertile (OR=3.14, 95% CI: 1.431–6.888, p=0.004) (Table 4).

Relationship between $1,25(OH)_2D_3$ and PTH in calcium SFs vs. controls

The mean PTH and $1,25(OH)_2D_3$ were 28.0±14.4 pg/mL, 52.5±19.0 ng/mL in calcium SFs and 27.8±10.8 pg/mL, 18.4±7.3 ng/mL in controls (p=0.871, p<0.001, respectively). $1,25(OH)_2D_3$ levels were significantly higher in calcium SFs than in controls (p<0.001). No correlation was found between $1,25(OH)_2D_3$ and PTH in calcium SFs (R=0.005, p=0.929). In controls, the $1,25(OH)_2D_3$ levels were inversely correlated with PTH levels (R=-0.269, p=0.001) (Fig. 1).

DISCUSSION

In the present study, an assessment of the roles of $1,25(OH)_2D_3$ and PTH in calcium stone formers revealed a correlation between $1,25(OH)_2D_3$ and PTH levels and urinary calcium excretion. $1,25(OH)_2D_3$ levels were significantly increased in calcium SFs compared to controls, and the balance between $1,25(OH)_2D_3$ and PTH was altered in calcium SFs.

Hypercalciuria is the most common metabolic abnormality in patients with urolithiasis.[10] Calcium oxalate overgrowth on plaque is due to calcium oxalate supersaturation, which is strongly linked to hypercalciuria.[13] The present data showing a strong correlation between serum $1,25(OH)_2D_3$ and PTH levels and urinary calcium excretion suggested that urinary calcium excretion might be affected by intrinsic factors such as serum $1,25(OH)_2D_3$ and PTH, as well as environment factors such as sodium intake.

Calcium regulates a wide range of biological processes and is one of the principal constituents of bone. The maintenance of adequate concentrations of calcium in the extracellular fluid requires the activity of two hormones, $1,25(OH)_2D_3$ and PTH.[12] PTH, which functions through a negative feedback loop to regulate extracellular calcium levels, is secreted in response to hypocalcemia and stimulates the release of calcium from bone, decreases the urinary loss of calcium, and indirectly stimulates calcium absorption in the small intestine by stimulating the synthesis of $1,25(OH)_2D_3$.[12]

The relationship between 25(OH) vitamin D_3 (calcidiol)

Table 3. Relationships between Urinary Calcium Excretion and Clinical and Laboratory Parameters

	Spearman correlation		Linear regression	
	Correlation (r)	*p* value	Standard coefficient	*p* value
Age (yrs)	-0.065	0.241		
Sex (male/female)	-0.069	0.213		
BMI (kg/m^2)	0.149	0.007	-0.024	0.572
Family history	0.012	0.831		
Stone episode	0.151	0.006	0.083	0.045
Serum				
Sodium	0.030	0.595		
Calcium	0.086	0.120		
Phosphate	-0.020	0.715		
Uric acid	-0.054	0.331		
$1,25(OH)_2D_3$	0.347	<0.001	0.259	<0.001
PTH	-0.193	<0.001	-0.160	<0.001
24 hrs urine				
Total volume	0.305	<0.001	-0.051	0.292
Sodium	0.502	<0.001	0.270	<0.001
Phosphate	0.469	<0.001	0.192	<0.001
Magnesium	0.375	<0.001	0.039	0.346
Citrate	0.277	<0.001	0.073	0.106
Oxalate	-0.019	0.727		
Uric acid	0.553	<0.001	0.243	<0.001
pH	0.170	0.002	0.027	0.525

BMI, body mass index; $1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3; PTH, parathyroid hormone; pH, potential of hydrogen.

Table 4. Results of Logistic Regression in Calcium Stone Formers Considering Hypercalciuria as the Dependent Variable According to Tertiles of Serum $1,25(OH)_2D_3$ as the Independent Variable

$1,25(OH)_2D_3$ (ng/mL)	Normocalciuria (n=274)	Hypercalciuria (n=52)	OR (95% CI)	*p* value
Mean±SD	50.8±17.9	61.3±21.9		<0.001
≤42.2	99 (36.1)	10 (19.2)	1	
>42.2 to ≤58.9	93 (34.0)	16 (30.8)	1.703 (0.736–3.942)	0.214
>58.9	82 (29.9)	26 (50)	3.139 (1.431–6.888)	0.004
P_{trend}				0.003

$1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3; ORs, odds ratios; CI, confidence interval; SDs, standard deviations.

levels and hypercalciuria has been reported previously.[14,15] However, some studies reported a weak correlation between calcium excretion and the level of 25(OH) vitamin D_3.[16] In reality, $1,25(OH)_2D_3$ is considered to be more important compared to $25(OH)D_3$ for mediating the biological actions of vitamin D on calcium and bone metabolism.[17] In the present study, a strong relationship between $1,25(OH)_2D_3$ and urinary calcium excretion was observed. Moreover, the hypercalciuric group had higher levels of $1,25(OH)_2D_3$ than the normocalciuric group. Hess and Jaeger[18] reported that patients with idiopathic hypercalciuria had higher serum concentrations of $1,25(OH)_2D_3$ than normocalciuric SFs. Furthermore, in the present study, $1,25(OH)_2D_3$ was significantly increased in calcium SFs compared to controls. Shakhssalim, et al.[19] also reported that the serum $1,25(OH)_2D_3$ levels in renal SFs were higher than in the control groups.

PTH stimulates the metabolism of $1,25(OH)_2D_3$ to its active hormonal form, $1,25(OH)_2D_3$ in the kidney. $1,25(OH)_2D_3$ promotes the absorption of calcium in the small intestine and calcium resorption in bone.[20] Although the functions of $1,25(OH)_2D_3$ and PTH are closely associated, a correlation between the levels of $1,25(OH)_2D_3$ and PTH was not observed in the current study. Alterations in the balance between PTH and $1,25(OH)_2D_3$ could be an important factor in calcium stone formation in calcium SFs.

PTH also correlated negatively with urinary calcium excretion. However, based on the exclusion of patients with hyperparathyroidism, this correlation was considered to be part of the normal process of homeostasis of hypercalciuria. Hess and Jaeger[18] reported that primary intestinal hyperab-

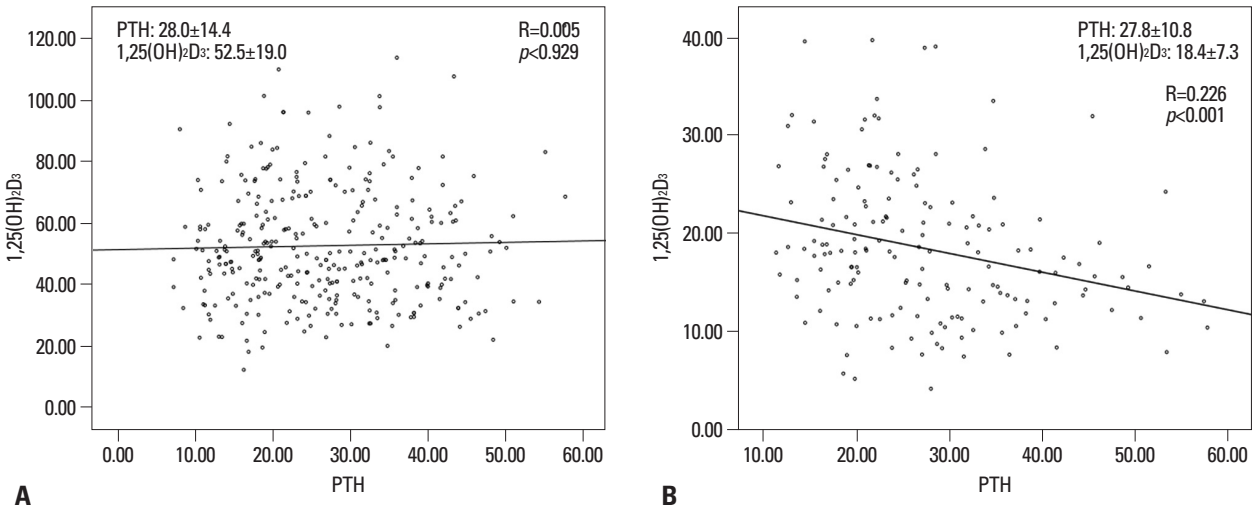

Fig. 1. Correlation between $1,25(OH)_2D_3$ and PTH (A) in calcium stone formers and (B) in controls. $1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3; PTH, parathyroid hormone.

sorption of calcium led to the depression of PTH secretion and PTH level was lower in hypercalciuric SFs compared to normocalciuric SFs at the same blood Ca^{2+} levels.[21] Similarly, PTH was lower in hypercalciuric SFs than in normocalciuric SFs in the current study, although the difference between the two groups did not reach statistical significance.

In the present study, multiple regression analysis revealed a positive correlation between $1,25(OH)_2D_3$ and urinary calcium excretion. Shakhssalim, et al.[19] also reported that $1,25(OH)_2D_3$ was an important hormone in the pathogenesis of recurrent renal calcium stone disease and could increase the risk of renal stone development by increasing urinary calcium and phosphorus excretion. However, no studies addressing the correlation between $1,25(OH)_2D_3$ and PTH in calcium SFs have been published to date. In our study, $1,25(OH)_2D_3$ level was positively correlated with urinary calcium excretion and higher in calcium SFs than in controls. However, the association between $1,25(OH)_2D_3$ and PTH in calcium SFs was not found. Presumably, these findings suggest that altered regulation of $1,25(OH)_2D_3$ rather than PTH might be the primary intrinsic factor for pathogenesis in calcium SFs.

There are several limitations to the present study. First, absorptive, renal induced, and resorptive hypercalciuria are common types of hypercalciuria.[22] The exclusion of patients with primary hyperparathyroidism from the study resulted in the exclusion of resorptive hypercalciuria. However, renal induced hypercalciuria could not be excluded because we did not perform a calcium load test. Nevertheless, due to the low prevalence of renal hypercalciuria, the difference is considered to be insignificant. Second, occupation and seasonal variation were not considered in this study despite the importance of the effect of skin exposure to sunlight on $1,25(OH)_2D_3$ levels. Parry and Lister[23] reported increased exposure to sunlight as the most likely cause of hypercalciuria. Third, This study was performed by cross-sectional manner and therefore, causality cannot be determined. It may be the idiopathic hypercalciuria which is causing the increasing the $1,25(OH)_2D_3$, and not the other way around. However, this would be unlikely seen from our result that PTH was actually negatively associated with urinary calcium excretion. Finally, these results alone cannot reach the mechanism by what calcium SFs have elevated $1,25(OH)_2D_3$ and future studies will need to be considered.

In conclusion, the present study is the first to examine the relationship between serum $1,25(OH)_2D_3$ and PTH in calcium SFs. $1,25(OH)_2D_3$ was closely correlated with urinary calcium excretion levels. Increased $1,25(OH)_2D_3$ levels were observed in the hypercalciuric group as well as in recurrent SFs. In calcium SFs, the $1,25(OH)_2D_3$ level was high and was not correlated with PTH levels. These findings suggest that $1,25(OH)_2D_3$ might be an important intrinsic factor in calcium stone formation.

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