Role of 1,25-Dihydroxy Vitamin D₃ 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 D₃ [1,25(OH)₂D₃] 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ (\( R = 0.005, \ p = 0.929 \)) in calcium SFs, while a negative correlation was found in controls (\( R = -0.269, \ p = 0.001 \)). Conclusion: 1,25(OH)₂D₃ was closely correlated with urinary calcium excretion, and high 1,25(OH)₂D₃ levels were detected in the hypercalciuric group and in recurrent SFs. However, 1,25(OH)₂D₃ was not correlated with PTH in calcium SFs. These findings suggest that 1,25(OH)₂D₃ might be important intrinsic factor for altered calcium regulation in SFs.

Key Words: 1,25-dihydroxy-vitamin D₃, 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.
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)2D3 which was performed at the same time. Intact PTH was measured with an immuno-radiometric assay with an ELSA-PTH kit (CIS Bio International, Paris, France), and 1,25(OH)2D3 levels were also measured with a radioimmunoassay with a 1,25(OH)2D3 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)2D3 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)2D3, and urinary biochemical parameters were compared in each group. The correlation between PTH or 1,25(OH)2D3 and serum and urinary metabolites and the correlation between PTH or 1,25(OH)2D3 and urinary calcium excretion in calcium stone formers (SFs).
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/m². The mean serum calcium, phosphate, uric acid, PTH, and 1,25(OH)₂D₃ 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)₂D₃ or PTH and clinico-laboratory parameters
1,25(OH)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ level (r=0.347, p<0.001), 24 h urine total volume (r=0.149, p=0.007), and 1,25(OH)₂D₃ level (r=0.355, p<0.001). However, in the multiple linear regression analysis, the 1,25(OH)₂D₃ level was correlated significantly only with 24 h urine calcium excretion (β=0.355, p<0.001).

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Table 1. Relationships between Serum 1,25(OH)₂D₃ or PTH Levels and Clinical and Laboratory Parameters

|                      | Serum 1,25(OH)₂D₃ |                      | 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)    | -0.026 | 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)₂D₃      | -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)₂D₃: 1,25-dihydroxy vitamin D₃; PTH, parathyroid hormone; BMI, body mass index; pH, potential of hydrogen.
association between vitamin D and calcium excretion. According to calciuria, serum parathyroid hormone (PTH) was altered in calcium stone formers. The present data show that urinary calcium excretion might be affected by intrinsic factors such as serum 1,25(OH)2D3 and PTH levels and urinary calcium excretion. 1,25(OH)2D3 levels were significantly increased in calcium SFs compared to controls, and the balance between 1,25(OH)2D3 and PTH was altered in calcium SFs. Hypercalciuria is the most common metabolic abnormality in patients with urolithiasis. Calcium oxalate overgrowth on plaque is due to calcium oxalate supersaturation, which is strongly linked to hypercalciuria. The present data showing a strong correlation between serum 1,25(OH)2D3 and PTH levels and urinary calcium excretion suggested that urinary calcium excretion might be affected by intrinsic factors such as serum 1,25(OH)2D3 and PTH, as well as environmental 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)2D3 and PTH. 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)2D3.

The relationship between 25(OH) vitamin D3 (calcidiol) and PTH in calcium stone formers revealed a correlation between 1,25(OH)2D3 and PTH levels and urinary calcium excretion. 1,25(OH)2D3 levels were significantly increased in calcium SFs compared to controls, and the balance between 1,25(OH)2D3 and PTH was altered in calcium SFs.

In the present study, an assessment of the roles of 1,25(OH)2D3 and PTH in calcium stone formers revealed a correlation between 1,25(OH)2D3 and PTH levels and urinary calcium excretion. 1,25(OH)2D3 levels were significantly increased in calcium SFs compared to controls, and the balance between 1,25(OH)2D3 and PTH was altered in calcium SFs.

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The relationship between 25(OH) vitamin D3 (calcidiol)
Renal SFs were higher than in the control groups. PTH stimulates the metabolism of 1,25(OH)\(_2\)D\(_3\) to its active hormonal form, 1,25(OH)\(_2\)D\(_3\) in the kidney. 1,25(OH)\(_2\)D\(_3\) promotes the absorption of calcium in the small intestine and calcium resorption in bone. 20 Although the functions of 1,25(OH)\(_2\)D\(_3\) and PTH are closely associated, a correlation between the levels of 1,25(OH)\(_2\)D\(_3\) and PTH was not observed in the current study. Alterations in the balance between PTH and 1,25(OH)\(_2\)D\(_3\) 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 patients with idiopathic hypercalciuria had higher serum concentrations of 1,25(OH)\(_2\)D\(_3\) than normocalciuric SFs. Furthermore, in the present study, 1,25(OH)\(_2\)D\(_3\) was significantly increased in calcium SFs compared to controls. Shakhssalim, et al.\(^{19}\) also reported that the serum 1,25(OH)\(_2\)D\(_3\) levels in renal SFs were higher than in the control groups.

### 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)\(_2\)D\(_3\) | 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               | 0.164 |
| 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)\(_2\)D\(_3\), 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)\(_2\)D\(_3\) as the Independent Variable

| 1,25(OH)\(_2\)D\(_3\) (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\(_{\text{trend}}\)        |                        |                       | 0.003       |         |

1,25(OH)\(_2\)D\(_3\), 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.\(^{16}\) In reality, 1,25(OH)\(_2\)D\(_3\) 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)\(_2\)D\(_3\) and urinary calcium excretion was observed. Moreover, the hypercalciuric group had higher levels of 1,25(OH)\(_2\)D\(_3\) than the normocalciuric group. Hess and Jaeger\(^{18}\) reported that patients with idiopathic hypercalciuria had higher serum concentrations of 1,25(OH)\(_2\)D\(_3\) than normocalciuric SFs. Furthermore, in the present study, 1,25(OH)\(_2\)D\(_3\) was significantly increased in calcium SFs compared to controls. Shakhssalim, et al.\(^{19}\) also reported that the serum 1,25(OH)\(_2\)D\(_3\) levels in
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in calcium SFs. 1,25(OH)₂D₃ was closely correlated with urinary calcium excretion levels. Increased 1,25(OH)₂D₃ levels were observed in the hypercalciuric group as well as in recurrent SFs. In calcium SFs, the 1,25(OH)₂D₃ level was high and was not correlated with PTH levels. These findings suggest that 1,25(OH)₂D₃ might be an important intrinsic factor in calcium stone formation.

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