Effect of Vitamin D Repletion on Urinary Calcium Excretion among Kidney Stone Formers

David E. Leaf,* Ruslan Korets, Eric N. Taylor, Jie Tang, John R. Asplin, David S. Goldfarb,** Mantu Gupta, and Gary C. Curhan†

Summary

Background and objectives Despite the important role of vitamin D in maintaining bone health, many clinicians are reluctant to treat vitamin D deficiency in kidney stone formers because of the theoretical risk of increasing urinary calcium excretion. This study examined the effect of vitamin D repletion on urinary calcium excretion among stone formers.

Design, setting, participants, & measurements Participants (n=29) were recruited from urology clinics affiliated with New York Presbyterian Hospital. Enrollment criteria included a history of nephrolithiasis, urinary calcium excretion between 150 and 400 mg/d, and a serum 25-hydroxyvitamin D level <30 ng/ml. Participants were given oral ergocalciferol (50,000 IU/wk) for 8 weeks. Serum and 24-hour urine tests were repeated after 8 weeks.

Results Levels of 25-hydroxyvitamin D increased significantly after vitamin D repletion (17 ± 6 and 35 ± 10 ng/ml, P < 0.001), but mean 24-hour urinary calcium excretion did not change (257 ± 54 and 255 ± 88 mg/d at baseline and follow-up, respectively, P = 0.91). However, 11 participants had an increase in urinary calcium excretion ≥20 mg/d; these participants also had an increase in urine sodium excretion, likely reflecting dietary variability. No participant experienced adverse effects from vitamin D, including hypercalcemia.

Conclusions Among stone formers with vitamin D deficiency, a limited course of vitamin D repletion does not seem to increase mean urinary calcium excretion, although a subset of individuals may have an increase. These data suggest that vitamin D therapy, if indicated, should not be withheld solely on the basis of stone disease, but 24-hour urinary calcium excretion should be monitored after repletion.


Introduction

Despite the important role of vitamin D in maintaining bone health, as well as a variety of other physiologic functions (1), many clinicians are reluctant to treat vitamin D deficiency or insufficiency in kidney stone formers because of the theoretical risk of increasing urinary calcium excretion. This reluctance likely derives from the fact that vitamin D is often cited as a risk factor for kidney stones (2), and epidemiologic studies have reported associations between urinary calcium excretion and serum levels of 25-hydroxyvitamin D [25(OH)D] (3) and 1,25-dihydroxyvitamin D [1,25(OH)2D] (4). However, although hypervitaminosis D is a well known cause of hypercalcemia and hypercalciuria, we are unaware of any prospective study in which the effects of standard replacement doses of vitamin D on urinary calcium excretion have been investigated among stone formers (5).

However, multiple studies have examined the effects of vitamin D supplementation among nonstone formers and have consistently failed to show an increase in urinary calcium excretion (6–8). Accordingly, the current study was conducted to examine whether vitamin D repletion adversely affects urinary calcium excretion specifically among stone formers.

Materials and Methods

Study Design

We conducted an interventional study of vitamin D repletion among outpatients followed at New York Presbyterian Hospital (NYPH) Columbia University Medical Center. All protocols were approved by the Columbia University Medical Center Institutional Review Board.

Study Participants

Participants consisted of adult outpatients followed in the metabolic stone clinic of investigator M.G. Inclusion criteria were (1) a history of nephrolithiasis as per medical records, (2) urinary calcium excretion between 150 and 400 mg/d measured within 3 months of enrollment, and (3) 25(OH)D deficiency or insufficiency (defined as a serum level <30 ng/ml) measured within 3 months of enrollment. Seven exclusion criteria were used. (1) Known uric acid, cystine, or struvite stone disease (although participants who had passed both uric acid and calcium oxalate stones or stones of mixed composition that consisted predominantly of calcium were eligible). (2) Hypercalcemia (defined as serum calcium >10.4 mg/dl) measured within 3 months of enrollment. (3) Acute stone
event or gross hematuria within 2 months of enrollment. (4) Any urologic intervention within 1 month of enrollment. (5) Suspected or known secondary causes of hypercalcemia, such as primary hyperparathyroidism, sarcoidosis, hyperthyroidism, or malignancy. (6) Addition or dose change of medicines potentially affecting uric acid since the baseline 24-hour urine collection. (7) Pregnancy.

Study Procedures

Patients with kidney stone disease followed at NYPH’s urology clinics are encouraged to provide urine and serum samples before their visits as part of routine care. Accordingly, patients meeting the above criteria were identified by a focused screening of electronic medical records before their scheduled visit to an NYPH-affiliated urology clinic. On the day of their scheduled visits, patients agreeable to discussing the research study were screened for symptoms suggesting active stone disease, recent urologic interventions, addition or dose change of medicines affecting urinary calcium excretion, and possible causes of secondary hypercalcemia. Those patients deemed eligible and wishing to enroll in the study provided written informed consent.

Vitamin D (erocolcalcerol 50,000 IU orally once weekly for 8 weeks) was dispensed to participants by the NYPH research pharmacy. Participants were asked to complete the following blood and urine tests at baseline and 8-week follow-up visits: serum basic metabolic panel, intact parathyroid hormone (PTH), 25(OH)D (sum of D2 and D3), and 24-hour urine collection for a comprehensive metabolic stone panel (Litholink, Chicago, IL). On completion of the study, participants were seen in the clinic to review their results as well as inquire about medication adherence and any symptoms suggestive of adverse medication effects.

To minimize large changes in urinary calcium excretion because of changes in diet, participants were asked to record a detailed diet log on the day of their baseline urine collection and try to replicate, to the best of their abilities, their baseline diet during the subsequent urine collection. To help participants achieve this replication, a diet log template was distributed. We have previously reported on our experience using this approach, and we have found it to be a reliable way of minimizing diet variability (9). We did not collect the diet logs or attempt to analyze diet composition; their purpose was simply to help participants replicate their diets during the urine collection periods.

Outcome Measures

The primary outcome measure was change in 24-hour urinary calcium excretion. Secondary outcome measures included changes in other 24-hour urine factors, including oxalate, citrate, uric acid, phosphorus, and sodium, as well as change in serum 25(OH)D.

Safety Monitoring

The primary safety concerns included serum calcium, 24-hour urinary calcium excretion, and stone recurrence. For every 10 participants who completed the study, an interim data safety analysis was carried out by investigators D.E.L. and M.G. Additionally, participants were educated regarding potential, albeit rare, adverse effects of vitamin D, including nausea and anorexia, and were encouraged to immediately report any such effects to the primary investigator (D.E.L.). Participants were also asked to immediately report any symptoms suggestive of stone recurrence (flank pain or gross hematuria).

Statistical Analyses

Statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC). Power analysis was calculated with the following assumptions: mean 24-hour urinary calcium excretion = 300 mg/d, α = 0.05, and SD = 30. With a sample size of 30 participants, we estimated that we would have the statistical power of 0.94 and 0.99 to detect a change in 24-hour urinary calcium excretion of 20 and 25 mg/d, respectively.

Normally distributed continuous data are reported as mean ± SD, and within-group differences were assessed by a paired t test. Skewed continuous data are reported as median and interquartile range (25–75 percentiles), and within-group differences were assessed by the Wilcoxon signed-rank test. Correlations between changes in 24-hour urinary calcium excretion with other urinary and serum parameters were assessed using simple linear regression. Finally, a multivariable linear regression model was created to evaluate whether changes in 25(OH)D were predictive of changes in 24-hour urinary calcium excretion after adjusting for other variables, which were significant independent predictors of the latter. All comparisons are two-tailed, with P<0.05 considered significant.

Results

Baseline Characteristics

Thirty participants were enrolled. Twenty-nine participants completed the study, with one participant lost to follow-up. Baseline characteristics for the 29 participants who completed the study are shown in Table 1. The majority of participants were male. Most nonwhite participants, the vast majority (16/18) were Hispanic (there is a large community of Dominicans served by NYPH). None of the participants had an estimated GFR <60 ml/min per 1.73 m². Similar numbers of participants had vitamin D insufficiency (20–29 ng/ml) compared with deficiency (<20 ng/ml), and roughly similar numbers of participants had PTH levels above and within the normal range. Only a single participant was taking a thiazide diuretic.

Primary and Secondary Outcomes

Baseline and follow-up 24-hour urine and serum parameters are shown in Table 2. 25(OH)D levels increased in all 29 participants, with a mean ± SD increase of 18±10 ng/ml. However, only 20 of 29 participants had a follow-up 25(OH)D level >30 ng/ml. No significant change in mean urinary calcium excretion was observed with vitamin D supplementation. Similarly, no significant changes in any of the other 24-hour urine or other serum parameters were noted.

No significant change in serum PTH was noted. Selected subgroup analyses based on race (white versus nonwhite), baseline vitamin D status (deficiency versus insufficiency), and baseline PTH status (above or within the normal range) also failed to show any significant change in serum PTH with vitamin D repletion.
Change in Urinary Calcium by Subgroups

Point estimates and 95% confidence intervals (CIs) for change in 24-hour urinary calcium excretion by selected subgroups are shown in Figure 1. The results did not seem to differ within any subgroup. Additionally, the results did not seem to differ by race.

Change in Urinary Calcium and Urinary Sodium by Individual Participants

We observed a large variability in the direction and magnitude of change in urinary calcium excretion among participants (Figure 2A). Similarly, despite the use of a diet log, we also observed a large variability in urinary sodium excretion (Figure 2B). Among the 11 participants with an increase in urinary calcium excretion of ≥20 mg/d (median [interquartile range] increase of 90 [44–139] mg/d), urine sodium and urea nitrogen excretion also tended to increase (68 [5–80] mmol/d and 3.8 [–0.5 to 4.6] g/d, respectively), although the latter did not reach statistical significance. Among the six participants with the greatest increase in urinary calcium excretion (139 [105–154] mg/d), urine sodium and urea nitrogen excretion were not significantly increased (17 [217 to 61] mmol/d and 2.3 [1.9 to 4.1] g/d, respectively). In both of these subgroups, the increase in serum 25(OH)D with vitamin D repletion was comparable with the rest of the cohort.

Associations between Change in Urinary Calcium and Changes in Other Variables

Change in urinary calcium excretion was positively associated with changes in the following 24-hour urine variables: volume (40 mg/d increase in urinary calcium per L/d increase in volume, 95% CI=11–70, P=0.01), citrate (17 mg/d increase in urinary calcium per 100 mg/d increase in citrate, 95% CI=3–32, P=0.02), and sodium (8.2 mg/d increase in urinary calcium per 20 mmol/d increase in sodium, 95% CI=2.8–13.8, P=0.005). No significant associations were found with changes in any of the other urine or serum parameters. A scatter plot of change in 24-hour urinary calcium excretion versus change in 25(OH)D is shown in Figure 3. No significant association was found [2.15 mg/d increase in urinary calcium per 1 ng/ml increase in 25(OH)D, 95% CI=–1.49 to 5.78, P=0.24].

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter (n=29)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>48±12</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76</td>
</tr>
<tr>
<td>Race n (%)</td>
<td>white 11 (38)</td>
</tr>
<tr>
<td>Renal function (mean ± SD)</td>
<td>serum creatinine (mg/dl) 0.9±0.2 estimated GFR (ml/min per 1.73 m²) 93±18</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/ml) n (%)</td>
<td>0–9 4 (14) 10–19 13 (45) 20–29 12 (41)</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml) n (%)</td>
<td>≤51 17 (59) &gt;51 12 (41)</td>
</tr>
<tr>
<td>Urine calcium (mg/d) median (IQR)</td>
<td>259 (216–290)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

Table 2. Urine and serum parameters before and after vitamin D repletion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcium (mg)</td>
<td>257±54</td>
<td>255±88</td>
<td>0.91</td>
</tr>
<tr>
<td>oxalate (mg)</td>
<td>42±18</td>
<td>41±15</td>
<td>0.84</td>
</tr>
<tr>
<td>citrate (mg)</td>
<td>696±383</td>
<td>701±320</td>
<td>0.92</td>
</tr>
<tr>
<td>uric acid (g)</td>
<td>0.77±0.26</td>
<td>0.77±0.20</td>
<td>0.96</td>
</tr>
<tr>
<td>pH</td>
<td>6.3±0.5</td>
<td>6.2±0.4</td>
<td>0.31</td>
</tr>
<tr>
<td>sodium (mmol)</td>
<td>228±94</td>
<td>202±65</td>
<td>0.23</td>
</tr>
<tr>
<td>potassium (mmol)</td>
<td>72±33</td>
<td>68±28</td>
<td>0.53</td>
</tr>
<tr>
<td>phosphorus (g)</td>
<td>1.0±0.3</td>
<td>1.0±0.3</td>
<td>0.91</td>
</tr>
<tr>
<td>urea nitrogen (g)</td>
<td>13±4</td>
<td>13±4</td>
<td>0.69</td>
</tr>
<tr>
<td>sulfate (mEq)</td>
<td>47±19</td>
<td>44±14</td>
<td>0.38</td>
</tr>
<tr>
<td>creatinine (mg)</td>
<td>1896±479</td>
<td>1880±468</td>
<td>0.74</td>
</tr>
<tr>
<td>volume (L)</td>
<td>1.7 (1.5–2.5)</td>
<td>2.1 (1.4–2.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Supersaturation</td>
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<tr>
<td>calcium oxalate</td>
<td>8±4</td>
<td>7±3</td>
<td>0.34</td>
</tr>
<tr>
<td>calcium phosphate</td>
<td>1.5 (1.0–2.2)</td>
<td>1.2 (0.8–1.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>uric acid</td>
<td>0.5 (0.2–1.0)</td>
<td>0.6 (0.3–0.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum studies</td>
<td></td>
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<tr>
<td>25(OH)D (ng/ml)</td>
<td>17±6</td>
<td>35±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>calcium (mg/dl)</td>
<td>9.3±0.4</td>
<td>9.4±0.4</td>
<td>0.69</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>43 (27–60)</td>
<td>39 (28–59)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Values shown are mean ± SD for normally distributed data and median (interquartile range) for skewed data. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.
Finally, multivariable linear regression was used to evaluate whether change in 25(OH)D was predictive of change in 24-hour urinary calcium excretion after inclusion of the above three significantly associated variables. After inclusion of these three variables in the model, the relation between change in 25(OH)D and change in 24-hour urinary calcium excretion remained nonsignificant [1.10 mg/d increase in urinary calcium per 1 ng/ml increase in 25(OH)D, 95% CI=−1.44 to 3.65, \( P=0.38 \)].

Safety, Adverse Effects, and Adherence
Vitamin D supplementation was well tolerated, with no adverse effects reported and no incidents of symptomatic stone recurrence. No participant developed hypercalcemia. All participants reported 100% adherence to the study drug. All participants completed follow-up 24-hour urine and serum testing in a timely manner (within 2 weeks of finishing the study drug), with the exception of a single participant who waited 4.5 weeks to complete follow-up testing.
Discussion

This is the first documented prospective study of the effects of vitamin D repletion on urinary calcium excretion among stone formers. We found that vitamin D repletion, accomplished by administration of standard doses, does not seem to adversely affect 24-hour urine calcium excretion among individuals with vitamin D deficiency or insufficiency.

Patients with vitamin D deficiency and a history of kidney stones are often deprived of the established benefits of vitamin D repletion because of a theoretical concern of increasing their risk of stone recurrence (10). However, vitamin D repletion is likely to be of particular importance to stone formers, especially those patients with hypercalciuria. Not only is hypercalciuria an important risk factor for osteoporosis in the general population (11), but it also seems to be associated with even higher rates of bone loss among stone formers than nonstone formers (12).

Given the known effects of vitamin D on intestinal calcium reabsorption, it may seem surprising that vitamin D repletion did not increase urinary calcium excretion. There are at least two possible explanations for this finding. First, the tightly regulated conversion of 25(OH)D to 1,25(OH)2D by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) may have limited synthesis of the active form, thereby preventing excessive intestinal calcium reabsorption. Second, an increase in intestinal calcium reabsorption did occur but did not increase urinary calcium excretion, because the additional calcium was deposited in bone to restore bone mineral content (13).

Surprisingly, we did not find any evidence of PTH suppression by vitamin D repletion. Given the known urinary calcium-lowering effects of PTH, it is conceivable that, if PTH had fallen, urinary calcium excretion would have increased. Therefore, the lack of change in PTH could partly explain the lack of change in urinary calcium excretion. Interestingly, other studies of vitamin D repletion have also not consistently shown a decline in serum PTH (14). The lack of suppression of PTH in our study may have been influenced by the large proportion of Hispanic participants. There is growing data that the relation between vitamin D and PTH is different among whites and nonwhites, with the latter group suppressing PTH at lower levels of vitamin D (15).

Although overall urinary calcium excretion was unchanged with vitamin D repletion, 11 participants had increases in urinary calcium excretion ≥20 mg/d. Although urine sodium and urine urea nitrogen also tended to increase among these participants, reflecting dietary changes on follow-up urine collections, it is unclear whether the magnitude of increase in urinary calcium excretion can be fully attributable to these dietary changes alone. Because dietary logs were not collected, differences in dietary calcium intake could not be assessed and might be a plausible explanation for the above findings. The small sample size allowed for only select subgroup analyses to try to identify baseline risk factors predictive of an increase in urinary calcium excretion and found no associations with race, baseline serum 25(OH)D, or PTH.

Limitations of this study include large intragroup variations in urinary sodium and urinary calcium excretion despite the use of a diet log, a nonrepresentative population (overrepresentation of Hispanics relative to the general US population), a relatively short duration of follow-up (8 weeks), and a modest sample size. Our a priori sample size calculation provided a high degree of statistical power to detect clinically meaningful changes in urinary calcium excretion; however, interindividual variability in urinary calcium excretion was greater than anticipated, thus reducing our power to detect differences. An additional limitation is the lack of a control group, which would have allowed for firmer conclusions to be made about individual variability in urinary calcium excretion. Finally, nine participants did not attain a serum 25(OH)D level greater than 30 ng/ml by completion of the study. Although nearly all participants reported perfect medication adherence, nonadherence may nonetheless have contributed to these findings. Additionally, many of the participants received vitamin D supplementation between the winter months of December and February, during which time they would have likely received decreased sunlight exposure. Indeed, others have reported similar findings when administering oral ergocalciferol during the winter months (16).

Future studies of vitamin D repletion among stone formers should be performed to explore the generalizability of these results, including among patients with estimated GFR <60 ml/min per 1.73 m², a group that was not represented in the present study. Additionally, these studies should evaluate the long-term safety of vitamin D repletion among patients with kidney stones as well as directly evaluate its efficacy in improving bone health. Finally, measurement of other factors such as serum phosphate, 1,25(OH)2D, and fibroblast growth factor-23 before and after vitamin D repletion could shed additional light on the pathophysiology of bone disease among stone formers.

In conclusion, our results suggest that vitamin D can be repleted in stone formers without causing an increase in urinary calcium excretion. Given the known benefits of vitamin D therapy in maintaining bone health, the potential benefits for cardiovascular, autoimmune, and neoplastic disease, and the findings above suggesting that it is safe, we feel that vitamin D therapy, if otherwise indicated, should not be withheld simply on the basis of calcium stone disease or hypercalciuria.
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Disclosures
None.

References

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M.G. and G.C.C. contributed equally to this work.

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