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Vitamin D repletion does not alter urinary calcium excretion in healthy postmenopausal women

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Abstract

Objective—To evaluate, in a posthoc analysis of a previous study, whether vitamin D repletion in postmenopausal women with insufficient vitamin D increases urinary calcium excretion, as vitamin D therapy might contribute to hypercalciuria and calcium stones in susceptible individuals, and the effect of vitamin D on the risk of urolithiasis warrants attention.

Subjects and methods—We recruited 18 women at ≥ 5 years after menopause who had vitamin D insufficiency (serum 25(OH)-vitamin D, 16–24 mg/dL). We excluded women with a history of urolithiasis and kidney disease. Women had one calcium absorption study when vitamin D-insufficient, received vitamin D therapy, and completed a second calcium absorption study when vitamin D-replete. We fed subjects meals that mirrored the nutrient composition from self-reported 7-day diet diaries. To measure calcium absorption, we collected urine for 24 h during both visits.

Results—We achieved vitamin D repletion in all women (25(OH)-vitamin D before and after treatment, 22 and 63 mg/dL, respectively; $P < 0.001$). The mean calcium intake was 832 mg/day. Residual urine specimens were available for 16 women, allowing a measurement of 24-h urinary calcium. Calcium excretion did not change after vitamin D therapy (212 before vs 195 mg/day after; $P = 0.60$). Of four women with hypercalciuria (> 247 mg/day), calcium excretion decreased in three (377–312 mg/day, not significant).

Conclusion—Vitamin D supplementation did not increase the urinary calcium excretion in healthy postmenopausal women. Many stone formers are at risk of premature bone loss, vitamin D insufficiency, or both. Based on the present results we suggest a study of patients with hypercalciuria and nephrolithiasis to determine the risks of vitamin D therapy.

Keywords

vitamin D; calcium; kidney stones; urolithiasis

Introduction

The risk of lithogenesis from vitamin D supplementation in patients with nephrolithiasis is not well defined. Vitamin D supplementation might enhance calcium-stone formation by increasing intestinal calcium absorption and subsequent urinary calcium excretion. Increased

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urinary calcium excretion could promote urinary saturation with calcareous crystals, particularly calcium oxalate [1]. Some studies report an association between vitamin D intake and kidney stones [2,3], but others do not [4]. Similarly, some researchers [5] but not others [6] report positive correlations between 25(OH)-vitamin D (25(OH)D) and stone formation or risk of stone formation. Thus, clinicians typically recommend abstinence from vitamin D supplements in stone formers.

Vitamin D is synthesized in the skin on exposure to sunlight, is required for optimal calcium absorption and might also play a role in preventing cancer, certain autoimmune disorders and hypertension. Vitamin D insufficiency, defined as a serum 25(OH)D level of < 30 ng/mL, is endemic, especially in the northern latitudes and in the elderly [7]. Endemic low vitamin D levels probably result from minimal food sources of vitamin D and limited exposure to sunlight. Most Americans fail to achieve the adequate intake for vitamin D (5–15 µg or 200–600 IU/day for adults aged ≥ 19 years), as recommended by the Food and Nutrition Board of the Institute of Medicine [8].

Vitamin D is also pivotal in calcium absorption, and low levels can contribute to osteoporosis or osteomalacia. Hypercalciuric stone-formers have a higher risk of osteoporosis but vitamin D supplements are generally avoided for fear of increasing calciuria and therefore stone formation. In a post hoc analysis of a previously reported study [9], we evaluated whether vitamin D repletion in vitamin D-insufficient postmenopausal women increased urinary calcium excretion.

Subjects and methods

The present study was a post hoc analysis of a recent report by Hansen *et al.* [9], in which the primary study outcome was the change in calcium absorption with correction of vitamin D insufficiency. In all, 18 postmenopausal women who were not stone-formers were recruited. The University of Wisconsin-Madison Institutional Review Board approved the study protocol, and all participants signed informed consent. Eligible women were ≥ 5 years past menopause and with vitamin D insufficiency, defined as a serum 25(OH)D level of 16–24 ng/mL by reverse-phase HPLC assay. We excluded women with hypercalcaemia, urolithiasis, inflammatory bowel disease, malabsorption, chronic diarrhoea, use of antibiotics within the past month, renal insufficiency (serum creatinine > 2.0 mg/dL), osteomalacia, hypercalciuria (defined as a spot urine calcium : creatinine ratio of > 0.25 at the screening visit), or a daily calcium intake of ≥ 1100 mg/day from diet and supplements, based on a calcium questionnaire completed at screening. The use of oral steroids, anticonvulsants, bisphosphonates, oestrogen compounds, calcitonin, or teriparatide within the past 6 months were also exclusion criteria. Finally, women were excluded if they had a previous adult wrist, hip or vertebral fracture, or a baseline T-score of – 3.0 at the lumbar spine or femur. All 18 women had 24-h urine samples collected to measure calcium absorption [9], but only 16 had residual samples allowing the additional urine calcium tests for the current study. Table 1 summarizes the baseline characteristics of the 16 subjects.

Each subject had vitamin D repletion with 50 000 IU of ergocalciferol (Tishcon, Inc., Westbury, NY, USA) daily for 15 consecutive days. Ergocalciferol (vitamin D₂) was chosen as similar doses of cholecalciferol (vitamin D₃) are not available by prescription in the USA. Vitamin D repletion (serum 25(OH)D ≥ 35 ng/mL, by HPLC) was confirmed by phlebotomy. The absence of toxicity was confirmed by normal serum calcium and spot urine calcium : creatinine ratios.

Subjects completed two 24-h stays in the General Clinical Research Center at the University of Wisconsin Hospital. For each stay, women arrived in the morning in the fasted state, and

fasting blood and urine samples were obtained. Women received dual stable calcium isotopes to trace calcium absorption, as previously described [9]. For the next 24 h, research nurses oversaw the collection of all urine produced.

During each stay, we fed women with meals selected by the bionutritionist to match their typical daily macro- and micronutrient intake, based on 7-day weighed food records completed by subjects before the first stay. The bionutritionist analysed food records using The Food Processor software (ESHA Research, Inc., Salem, OR, USA). For each woman the nutritionist estimated the mean daily intake of calcium, energy, macronutrients, fibre, vitamin D, sodium, iron, magnesium, potassium, phosphorus, oxalate, and caffeine. Subsequently, the nutritionist selected subjects' hospital meals based on her outpatient nutritional habits, so that any changes in calcium absorption would relate to changes in vitamin D status rather than changes in nutrient intake. We calculated the potential renal acid load (PRAL) of each woman's diet [10,11]. Meals during the second overnight stay were identical to those served during the first (Table 1).

The General Medical Laboratory (Madison, WI) measured serum and urine chemistry. Total serum 25(OH)D was measured in the University of Wisconsin Osteoporosis Research Laboratory by a semi-automated solid-phase extraction reverse-phase HPLC assay [9]. Concentrations and ratios of calcium isotopes in the 24-h urine samples were quantified by high-resolution inductively coupled plasma mass spectrometry.

Differences in urinary calcium values before and after repletion were assessed using a paired Student's *t*-test. We used Spearman's correlation coefficient to investigate patient variables associated with biochemical and urinary changes after vitamin D repletion, with differences for all assessments considered statistically significant with a two-sided $P < 0.05$.

Results

All 18 women achieved vitamin D repletion, defined as a serum 25(OH)D level of > 35 ng/mL after ergocalciferol therapy [9] (Table 1). Fractional calcium absorption increased with vitamin D repletion ($P = 0.04$) [9] while serum parathyroid hormone and serum calcium levels remained stable (Table 1). The 24-h urinary calcium excretion and spot urine calcium : creatinine ratios remained unchanged, despite high-normal serum 25(OH)D levels and a corresponding increase in calcium absorption (Table 1).

Figure 1 shows the subjects' mean 24-h urinary calcium excretion before and after vitamin D therapy, and Fig. 2 the 24-h urinary calcium excretion measures for subjects with paired measures before and after treatment (as the samples from two were lost, and as two additional subjects were missing the 24-h urine collection either before or after therapy, giving 12 individual paired comparisons). Four subjects had hypercalciuria (> 247 mg calcium/day) based on 24-h urine measurements before vitamin D repletion. In these four women, the mean (SEM) 24-h urinary calcium excretion did not change, being 377 (66) and 312 (20) mg/day before and after treatment, respectively ($P = 0.32$).

We explored dietary factors associated with urine calcium excretion using multivariate analysis. There was no association between urine calcium excretion and dietary caffeine, protein or PRAL. The only dietary factor associated with urinary calcium excretion was oxalate, and this became apparent only after stratification by calciuric status. There was an inverse association between urinary calcium excretion and oxalate intake in four subjects with hypercalciuria ($R = -0.29$). These women had a lower mean oxalate intake than those without hypercalciuria ($P = 0.003$; 95% CI 0.570–0.921).

Discussion

Experts recommend adequate vitamin D stores throughout the year to prevent secondary hyperparathyroidism and bone loss. However, vitamin D is thought to exacerbate hypercalciuria in susceptible individuals. Notably, studies disagree on whether vitamin D supplementation induces or exacerbates hypercalciuria [12].

The goal of the present study was to examine the effect of vitamin D repletion on the urinary calcium excretion. We evaluated this in postmenopausal women with initial vitamin D insufficiency who had vitamin D repletion to high-normal 25(OH)D levels. The results showed that vitamin D repletion did not alter urinary calcium excretion, despite increased calcium absorption [9]. Our results differ from previous studies in which vitamin D supplementation and/or status was associated with increased urinary calcium excretion [1–3,5]. However, our study results agree with others in which urinary calcium excretion was not altered by vitamin D therapy, based on 24-h urine calcium or urine calcium : creatinine ratios [4,6,13,14]. Interestingly, among four women with hypercalciuria at baseline in our study, urinary calcium excretion did not increase. We therefore suggest that vitamin D supplementation might be safe for women with hypercalciuria, assuming close observation of the various calcium lithogenesis risk factors.

Calcium metabolism and the control of urinary calcium excretion are regulated by many factors, of which vitamin D is only one. Indeed, evidence suggests that various nutrient–gene interactions involving vitamin D might influence urinary calcium excretion. One study suggested that a high-protein, high-sodium diet in postmenopausal women, considered typical for many women in the USA, detrimentally affects calcium and bone metabolism in those with a certain vitamin D-receptor genotype [15]. A recent study in rats showed that hypercalciuria occurred with vitamin D treatment only when they were fed a chronic high dietary acid load, suggesting that vitamin D treatment, even in high dosages, does not lead to hypercalciuria unless other dietary risk factors are present [16]. Given these data, we theorise that the risk of hypercalciuria from vitamin D supplementation, using accepted blood measures of vitamin D adequacy as outcome variables, might be smaller than the risks from innumerable different combinations of genetic and dietary alterations that could contribute to altered calcium transport in the intestine, kidney and bone [17]. As the importance of vitamin D in human nutrition and health appears to be growing [18], withholding vitamin D supplements from stone formers who would benefit from an optimization of their vitamin D status might be unwarranted. The elucidation of major dietary and other effectors of urinary calcium excretion thus continues to be a research question.

Postmenopausal women carry a higher risk of kidney stones than younger women; thus, they are a good subgroup for urolithiasis research. Additional strengths of the present study include the use of high-dose vitamin D₂ as the intervention, making this a unique study, and the 24-h urine collections, which were carefully timed and collected in a metabolic research unit. However, there are limitations to the conclusions from this study. First, the subjects were not stone-formers and thus might have responded differently to vitamin D repletion than would stone formers. Second, there were few subjects, suggesting caution in interpreting and extrapolating the results. Third, while there was no vitamin D effect on urinary calcium excretion in the study, other urinary variables associated with an increased risk of lithogenesis, such as supersaturation, were not measured. Regarding diet, although each woman's diet during her overnight stay on the research unit was matched to her usual dietary intake from 7-day diet records gathered and analysed by the study bionutritionist, it is possible that there was under-reporting of dietary sodium [19]. Therefore, the effect on urinary calcium excretion on vitamin D repletion in subjects with higher sodium intakes

should be further explored. Finally, the mean calcium intake of the subjects in the study was 830 mg/day. While this calcium intake is slightly higher than the average intake of postmenopausal American women [20], we cannot determine whether women with a higher calcium intake closer to recommended intake values (1000–1500 mg/day) [20] would develop hypercalciuria with vitamin D therapy.

In summary, our study suggests that vitamin D supplementation can be provided to postmenopausal women who are not stone-formers and who are vitamin D insufficient, without fear of increased risk of nephrolithiasis. However, prospective, controlled studies are needed to assess the broader safety of vitamin D repletion in stone-forming subjects and women with high calcium intake. Given that the published reports vary in the assessment of hypercalciuria, and given that the urinary calcium : creatinine ratio is a measure of questionable value in accurately detecting hypercalciuria (Jones *et al.* manuscript submitted), such a study should evaluate the 24-h urinary excretion of calcium and related lithogenic risk factors. Also, we propose that vitamin D status be assessed using serum 25(OH)D (calcidiol), as experts support this measure [7]. Finally, we propose that future studies address whether there is a difference in urinary calcium excretion when vitamin D is provided as vitamin D₂ or vitamin D₃, as bioavailability might be different, and the dosage at which vitamin D supplementation or repletion is maximally effective and safe.

Acknowledgments

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Abbreviations

25(OH)D	25(OH)-vitamin D
PRAL	potential renal acid load

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Fig. 1.
The mean (SEM) 24-h urinary calcium excretion before and after vitamin D depletion in 16 subjects.

Fig. 2.

Individual calciuric responses to vitamin D repletion. Data shown are from 12 subjects with paired 24-h urinary calcium excretion measures before and after treatment with vitamin D₂; there was no change in the means for 24-h urinary calcium excretion for the group, at 212 (38) and 195 (22) mg/day, respectively; $P = 0.58$).

Table 1

The anthropometric, dietary, serum and urine measures of the subjects; differences between groups were not significant ($P > 0.05$) for any of the measures before and after treatment, except for serum 25(OH)D ($P < 0.001$) after treatment

Mean (SEM, range) variable	Before	After
Age, years	59 (1.7, 46–69)	
Body mass index, kg/m ²	29.3(1.5, 19.7–44.3)	
Dietary measures		
kcal, per day	1606 (95, 1154–2235)	1602 (98, 1152–2237)
Protein, g/day	74 (3.8, 52–96)	74 (3.9, 52–96)
Protein, % of total kcal	19 (1.0, 13–25)	19 (1.0, 13–25)
Carbohydrates, g/day	186 (14, 85–266)	185 (14, 85–266)
Carbohydrates, % of total kcal	46 (2.4, 27–62)	46 (2.4, 27–61)
Fat, g/day	65 (5.5, 29–93)	65 (5.7, 29–93)
Fat, % of total kcals	36 (2.0, 22–49)	36 (2.0, 23–49)
Fibre, g/day	16 (1.2, 9–22)	16 (1.2, 9–22)
Calcium, mg/day	832 (50, 578–1140)	830 (50, 569–1142)
Sodium, mg/day	2500 (160, 1377–3550)	2490 (160, 1374–3552)
Magnesium, mg/day	254 (16, 149–357)	253 (16, 143–351)
Potassium, mg/day	2189 (160, 1365–3349)	2175 (159, 1365–3350)
Phosphorus, mg/day	1109 (62, 728–1554)	1109 (63, 700–1557)
Vitamin D, IU/day*	93 (20, 15–274)	92 (20, 15–274)
Oxalate, servings/day [†]	0.79 (0.24, 0.03–2.8)	0.60 (0.18, 0.03–2.0)
Caffeine, servings/day [‡]	2.7 (1.0, 0–14)	2.8 (1.0, 0–14)
Fruits & veg, servings/day	5.0 (0.33, 1.7–10)	5.0 (0.33, 1.7–10)
PRAL, per day [¶]	14.1 (2.9, –4.3 to 28.8)	14.4 (2.9, –2.6 to 28.8)
25(OH)D, ng/mL	22.5 (1.1, 14–33)	64.7 (5.6, 36–129)
Parathyroid hormone, pg/mL	51.3 (3.8, 36–86)	48.3 (4.0, 29–78)
Calcium, mg/dL	9.4 (0.1, 8.7–9.8)	9.3 (0.1, 8.7–10)
Urine measures		
Spot calcium : creatinine ratio	0.126 (0.019, 0.046–0.360)	0.129 (0.015, 0.044–0.227)
24-h urinary calcium, mg/day	212 (37, 56–542)	195 (22, 110–370)

* Vitamin D in µg = IU/40;

[†] Oxalate intake was quantified on the basis of usual servings per day of foods known to be rich in oxalate, including spinach, Swiss chard, chocolate, tea, rhubarb, beets, peanut butter, peanuts, sunflower seeds, sesame seeds;

Caffeine intake was quantified as usual servings per day of caffeinated coffee, tea, or cola;

[‡] quantified from subjects' dietary intake of protein, phosphorus, potassium, magnesium, and calcium as described by Remer *et al.* [10,11]; the PRAL provides an estimate of endogenous acid production that exceeds the alkali produced for given foods ingested, and accounts for variable gastrointestinal absorption of nutrients and the amount of sulphate produced from metabolized proteins.