Vitamin D Supplementation and Risk of Hypercalciuria in Stone Formers

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Introduction. Whether administrating of vitamin D supplements increases the risk of hypercalciuria is still unanswered. The aim of the present study was to determine whether use of vitamin D supplementation might increase the risk of hypercalciuria.
Methods and Materials. This interventional study was conducted on 30 who suffered from vitamin D insufficiency and deficiency and also had a history of nephrolithiasis. The patients were treated with vitamin D supplement (50000 units per week for 2 months and then every 2 weeks until the end of the 3rd month). Serum and urinary biomarkers were measured at baseline and 3 months after start of vitamin D therapy.
Results. Administrating vitamin D supplement for 3 months led to a significant increase in serum level of 25-hydroxyvitamin D from 10.4 ± 4.2 ng/mL to 44.0 ± 10.7 ng/mL ($P < .001$). Also, the median level of serum parathyroid hormone was significantly reduced from 53 ng/L (interquartile range, 22 ng/L to 163 ng/L) to 38 ng/L (interquartile range, 16 ng/L to 102 ng/L; $P < .001$). There was also a significant increase in urinary citrate after using vitamin D supplement compared with the baseline from 341 mg (interquartile range, 90 mg to 757 mg) to 411 mg (interquartile range, 115 mg to 1295 mg; $P = .045$). Comparing biochemical parameters between the groups who developed 15% and greater and less than 15% increase in urinary calcium showed no significant difference after treatment.
Conclusions. The use of vitamin D supplements in conventional dose in patients with vitamin D deficiency may not lead to increased risk of hypercalciuria.

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INTRODUCTION

Nephrolithiasis is a common metabolic disease with an overall lifetime risk of 6% to 12% and a recurrence rate up to 50%.[1,2] Although its prevalence varies widely in different regions, recent studies have shown that its incidence is increasing worldwide mostly because of lifestyle and diet changes and also increased incidence of metabolic syndrome and diabetes mellitus. For instance, in the United States, the prevalence of kidney stones in both sexes has increased from 5.2% in 1994 to 8.8% in 2010.[3,4]

From the pathogenesis view, nephrolithiasis is regarded as a systemic and multifactorial disease that many factors including geographic area, racial distribution, socioeconomic status, dietary habits, genetic susceptibility, and underlying metabolic risk factors can affect its occurrence.[2] Hypercalciuria caused by either increased rate of urinary calcium excretion or reduced calcium reabsorption is the

most common metabolic abnormality seen in patients with urinary calcium stones.[2,5] Parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D3 are the main endocrine regulators of calcium homeostasis. Secretion of PTH, in response to hypocalcemia, causes an increase in serum calcium levels by directly stimulating both bone and renal reabsorption of calcium and indirectly through the synthesis of 1,25-dihydroxyvitamin D3 in the kidney and absorption of intestinal calcium.[6,7]

Studies have shown a simultaneous increase in serum level of active metabolite of vitamin D in patients who had an increased risk of nephrolithiasis, an observation that may suggest a link between vitamin D overdose and risk of calcium based stone formation.[7,8] Moreover, some recent studies suggest an association between increased 1,25-dihydroxyvitamin D3 serum levels and intestinal calcium hyperabsorption which may further contribute to hypercalciuria and ultimately stone formation.[6,7] Despite these observations, there is no robust cause and effect association between serum levels of vitamin D and rate of nephrolithiasis.

The hypothesis related to the association between the use of vitamin D supplementation and elevated risk for nephrolithiasis has been recently raised based on recent observations on high prevalence of nephrolithiasis in patients requiring administration of vitamin D supplements. In fact, the episodes of hypercalcemia and hypercalciuria have shown to be common events in patients receiving calcium and vitamin D supplementation, regardless of the vitamin D dose or serum 25-hydroxyvitamin D level.[9] However, increased risk of hypercalciuria following administration of vitamin D supplements still remains questioned.[10] According to a recent systematic review by Tabrizi and colleagues, the prevalence of vitamin D deficiency and insufficiency in Iranian population is high.[11] In a multicenter study performed among different Iranian population,[12] the prevalence of vitamin D deficiency was about 60% in men older than 60 years old in Tehran.[12] However, the questionable association between administration of vitamin D and higher risk of nephrolithiasis makes it a healthcare challenge for physicians to whether prescribe vitamin D supplementation in stone former individuals.[13] Therefore, in this study, we aimed to determine whether vitamin D supplementation in active stone formers affects the risk of hypercalciuria.

MATERIALS AND METHODS

Patients

This interventional study was conducted on 30 consecutive active stone former patients aged 20 to 65 years referred to the Department of Nephrology or outpatient clinic of Dr Shariati Hospital in 2015 and suffered from vitamin D deficiency or insufficiency. Patients who were pregnant, had hypercalcemia (baseline calcium level, ≥ 10.4 mg/dL), were consuming medications that affect calcium and bone metabolism (such as calcium) or calcium excretion (such as steroidal or hormonal drugs), had previous history of primary hyperparathyroidism or other systemic diseases (cancer, alcoholic liver disease, and osteoporosis), and had invasive diagnostic or therapeutic interventions on renal stones within the month prior to enrollment, were excluded from study.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences and all participants signed the informed consent form before enrolling into the study (Clinical trial registration number, IRCT20180108038262N2). At the time of recruitment, all participants underwent physical examination and anthropometric information including age, history of kidney stones, and medications were collected.

Following enrollment into the study, eligible patients received vitamin D supplement (provided by Dana Pharmaceutical Company, Iran), 50000 units per week for 2 months, and then every 2 weeks until the end of the 3rd month. Patients were advised not to change their diet habits during this period as much as they could.

Laboratory Measurements

Height was measured with a stadiometer. Weight was measured on a calibrated beam balance. Blood pressure was measured using a standard calibrated mercury sphygmomanometer on the right hand after the participants had been sitting for at least 5 minutes. Venous blood samples were collected in the morning after 12 hours of fasting at 2 time points, the time of enrollment, and 3 months after starting the vitamin D supplementation. The blood samples were centrifuged and then serum was collected to measure the levels of calcium, creatinine, uric acid, 25-hydroxyvitamin D, and PTH hormone levels. The 24-hour urine also was collected for measurement of creatinine, citrate, oxalate, sodium,

uric acid, and calcium concentrations at the time of enrollment and 3 months after starting the vitamin D consumption. 25-Hydroxyvitamin D level was measured with a radioimmmunoassay method using a Roch kit.

Definitions

Vitamin D insufficiency and deficiency were defined as serum 25-hydroxyvitamin D level less than 30 ng/mL and less than 20 ng/mL, respectively.[14] Active stone formers were defined as those having at least 2 episodes of stone recurrence or increase in stone size within the past 5 years. Hypertensive patients were those who were on antihypertensive medications or had systolic blood pressure of 140 mm Hg and higher or diastolic blood pressure of 90 mm Hg and higher. A 15% or greater increase in urinary calcium compared to baseline was considered significant.

Statistical Analysis

Results were presented as mean ± standard deviation or median (1st and 3rd quartiles) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using the *t* test or the Mann-Whitney U test, whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using the chi square test. The change in chemical biomarkers after treatment compared with the baseline values was assessed using the paired *t* test or the Wilcoxon test. For the statistical analysis, the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA) was used. A *P* value less than .05 was considered significant.

RESULTS

In total, 30 consecutive patients were assessed. Out of them, 63.3% were men (n = 19). The mean age was 42 ± 9 years (range, 28 to 60 years). The mean body mass index was 25 ± 3 kg/m^2 (range, 20.5 kg/m^2 to 31.5 kg/m^2). Among them, 26.7% (n = 8) were hypertensive.

Anthropometric, clinical and laboratory characteristics of the patients at baseline and 3 months after vitamin D therapy are presented in Table 1. As it is indicated in Table 2, all the patients had vitamin D deficiency with a serum 25-hydroxyvitamin D level less than 20 ng/mL. Administration of vitamin D supplement for 3 months led to a significant increase in serum levels of 25-hydroxyvitamin D from 10.4 ± 4.2 ng/mL to 44.0 ± 10.7 ng/mL ($P < .001$) and a significant decrease in median level of serum PTH from 53 ng/L to 38 ng/L ($P < .001$). The only significant change in 24-hour urine parameters was an increase in urine citrate level changing from 341 mg (90 mg, 757 mg) to 411 mg (115 mg, 1295 mg) after 3 months of vitamin D treatment. A 15% or greater increase in urinary calcium compared to baseline was found in 53.3% of the patients (n = 16), although it was nonsignificant ($P = .62$). The effects of vitamin D supplementation on urine calcium are shown in Table 2. Divided the

Table 1. Patients' Characteristics

Variable	Value
Number of patients	30
Sex	
Male	19
Female	11
Mean age, y	42 ± 9
Mean body mass index, kg/m^2	25.1 ± 3.1
Hypertension, %	26.7

Table 2. Laboratory Biomarkers Before and After Vitamin D Supplementation

Parameters	Before Treatment	After Treatment	*P*
Mean serum creatinine, mg/dL	1.1 ± 0.3	1.0 ± 0.3	.07
Mean serum calcium, mg/dL	9.0 ± 0.3	9.1 ± 0.4	.54
Serum parathyroid hormone, ng/L	53 (23 to 163)	38 (16 to 102)	< .001
Mean serum vitamin D, ng/mL	10.4 ± 4.2	44.0 ± 10.7	< .001
Median 24-hour urine citrate, mg	341 (90 to 757)	411 (115 to 1295)	.045
Mean 24-hour urine uric acid, mg	513 ± 184	512 ± 186	.98
Mean 24-hour urine calcium, mg	186 ± 86	198 ± 98	.39
Mean 24-hour urine sodium, mEq/L	165 (30 to 400)	173 (19 to 416)	.62
Mean 24-hour urine oxalate, mg	36 ± 17	34 ± 14	.15

Table 3. Laboratory Biomarkers of Patients With and Without Urinary Calcium Increase, Before and After Vitamin D Supplementation

Parameters	Group With ≥ 15% Increase in Urinary Calcium (n = 16)			Group With < 15% Increase in Urinary Calcium (n = 14)		
	Before Treatment	After Treatment	*P*	Before Treatment	After Treatment	*P*
Serum vitamin D, ng/mL	10.7 ± 4.5	44.6 ± 10.0	.51	9.7 ± 3.7	53.5 ± 25.6	.20
Serum parathyroid hormone, ng/L	47.8 ± 19.9	47.6 ± 15	.19	61.4 ± 35.0	39.6 ± 23	.26
Urine sodium, mEq/L	174.6 ± 103	183 ± 100	.49	151.1 ± 78.0	158.0 ± 70	.44
Urine uric acid, mg	514.2 ± 208	545.2 ± 218.1	.97	512.5 ± 148	464.3 ± 117	.22
Urine calcium, mg	169 ± 90.0	225 ± 107.6	.17	212.4 ± 77.0	146.6 ± 57	.02

participants into 2 groups with 15% and greater and less than 15% increase in urinary calcium we found no significant changes in the parameters in these two groups after treatment (Table 3).

DISCUSSION

We found that administration of vitamin D supplements in patients who suffer from vitamin D deficiency, did not significantly lead to a 15% and greater increase in urinary calcium. In other words, administrating vitamin D supplements for three months may not influence excretion of urinary calcium in patients who suspected to renal stone disease. There are similar studies that could not demonstrate the increased risk of hypercalciuria following use of vitamin D supplements or increased serum level of vitamin D.[10,13] Leaf and colleagues[14] showed that the use of vitamin D supplement could not change the urinary level of calcium and thus could not increase the risk of renal stone formation. Similarly, as indicated by Gallagher and colleagues,[15] no relationship was found between hypercalciuria and vitamin D dose. More interestingly, episodes of hypercalciuria were either transient or recurrent. Contrary to our results, some studies have shown a significant dose dependent increase in the occurrence of nephrolithiasis by administrating vitamin D supplements. Zwart and coworkers[16] showed that regimen containing 250 µg/wk dose of vitamin D was safe. However, a regimen of 4 weekly followed by monthly doses of 1250 µg can raise the risk of hypercalciuria. Interestingly, some studies especially on animal models have shown that the use of vitamin D3 with calcium supplementation significantly decreased the formation of stones and caused a significant reduction in urinary calcium, suggesting a protective role for combination therapy.[17] In a study by Haghighi and colleagues, oral calcium, 1000 mg, and vitamin D, 400 U/d, in postmenopausal women for 1 year did not change blood and urinary levels of calcium.[18] Calcium and vitamin D could be used in kidney stone formers but blood and urinary biochemical profile should be assessed regularly.[19]

However, in a study by Jackson and colleagues,[20] an increased risk of kidney stone following combination therapy with vitamin D plus calcium was shown. This effect might be explained by an elevated levels of urinary calcium. In fact, the effects of vitamin D supplements on the risk of hypercalciuria still remain controversial, probably due to the differences in study protocol especially the dose and duration of vitamin D therapy in addition to intake of other sources of calcium. Altogether, this study showed that vitamin D intake with conventional dose was not significantly associated with increased risk of kidney stone, although higher risk with higher doses could not be excluded.

Our study has some limitations, including low number of the participants, short follow-up, and not having the food questionnaire in order to obtain the detailed diet habits of our participants. Therefore, to clarify the effects of vitamin D supplements on kidney stones, studies considering different doses of vitamin D administered for different durations are needed on larger population.

CONFLICT OF INTEREST

None declared.

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