25-Hydroxyvitamin D in the Range of 20 to 100 ng/mL and Incidence of Kidney Stones

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Objectives. Increasing 25-hydroxyvitamin D serum levels can prevent a wide range of diseases. There is a concern about increasing kidney stone risk with vitamin D supplementation. We used GrassrootsHealth data to examine the relationship between vitamin D status and kidney stone incidence.

Methods. The study included 2012 participants followed prospectively for a median of 19 months. Thirteen individuals self-reported kidney stones during the study period. Multivariate logistic regression was applied to assess the association between vitamin D status and kidney stones.

Results. We found no statistically significant association between serum 25-hydroxyvitamin D and kidney stones ($P = .42$). Body mass index was significantly associated with kidney stone risk (odds ratio = 3.5; 95% confidence interval = 1.1, 11.3).

Conclusions. We concluded that a serum 25-hydroxyvitamin D level of 20 to 100 nanograms per milliliter has no significant association with kidney stone incidence. (*Am J Public Health*. Published online ahead of print October 17, 2013: e1–e5. doi:10.2105/AJPH.2013.301368)

An issue of possible concern related to the use of vitamin D supplementation is a reported increase in risk of kidney stones.[1] Mounting evidence indicates that a 25-hydroxyvitamin D (25[OH]D) serum level in the range of 40 to 60 nanograms per milliliter (ng/mL) is needed for substantial reduction in risk of a wide range of diseases including breast cancer,[2] colorectal cancer,[3] multiple sclerosis,[4] and type 1 diabetes.[5,6] However, few people can achieve 25(OH)D in the range higher than 40 ng/mL without supplementation.[7]

GrassrootsHealth is a nonprofit public health research organization that runs a large population intervention study allowing participants to reach and sustain, if desired, a 25 (OH)D serum level of their choice and tracking subsequent health outcomes. GrassrootsHealth has assembled a database that includes information on serum 25(OH)D concentrations, demographic characteristics, and health status measures. These data include values from 5552 individuals with daily supplemental intakes averaging 3600 international units (IU) per day and an average 25(OH)D level of 45 ng/mL, which is higher than the ranges found in most other cohorts.[2,4]

In this study we investigated whether serum 25(OH)D concentration in the range of 20 to 100 ng/mL was associated with incidence of kidney stones in all participants who provided data at 2 or more sampling times.

METHODS

Participants were individuals who responded to an invitation issued to all attendees at a vitamin D seminar hosted by GrassrootsHealth in December 2008, and others who were recruited via the Internet. The only inclusion criterion for this study was that participants must have completely filled out at least 2 cohort survey questionnaires. All ages and both genders were included. Incidences of kidney stones were defined as participants having a self-reported kidney stone diagnosed within the study period. All incidences of kidney stones were adjudicated by medical records, e-mail correspondence, or phone interviews to affirm a kidney stone. For those who developed kidney stones, we analyzed data from their most recent serum collection and questionnaire before the kidney stone incident date, and among those who did not develop kidney stones we analyzed their most recent available serum sample and questionnaire data.

One of the investigators (C. F.) conducted the correspondence with those who developed kidney stones. The individuals were asked:

1. Was your kidney stone attack diagnosed by a physician? [If yes] What is the name and address of the physician or medical facility? [Interviewer then sent the individual a medical records release authorization form.]
2. Please describe the symptoms you had at the time of this attack. [Interviewer recorded all symptoms, such as sudden-onset flank pain, recorded severity of pain, and asked the individual to describe how the attack was resolved or ended.]

The definition of a kidney stone attack was a kidney stone attack either (1) diagnosed by a physician or (2) self-reported, with recurrence of the same symptoms as during the original presentation of the incident that was diagnosed by a physician as a kidney stone. To meet the definition, the individual must have reported severe pain of rapid onset in the flank, back, or both. The definition required no history of recent trauma to the back or abdomen, accident, or any alternative explanation for the pain of sudden onset. We obtained information on computed tomography scan; contrast x-ray studies of kidney, ureter, and bladder; ultrasound; and chemical analysis of the stones when available. We obtained medical records when consent was provided.

Of the 13 individuals with kidney stones in this investigation, 12 were diagnosed by a physician. The remaining individual had a history of physician-diagnosed kidney stones. During the current episode this individual reported passing a kidney stone in his urine

and retrieving it. His symptoms during this episode were the same as those he had when previously diagnosed with kidney stones by his physician, including severe pain in flank or back of rapid onset. He reported immediate and complete resolution of pain upon passing the stone. This individual had no history of trauma or alternative explanation for the pain.

We determined serum 25(OH)D concentrations by blood spot test kits analyzed by ZRT Laboratory (Beaverton, OR). The analytical method used was high-performance liquid chromatography followed by mass spectroscopy and has been validated against the DiaSorin Radioimmunoassay method with an R^2 value of 0.91 and with a slope not different from 1.0.[8] The intraassay coefficient of variation was 10%, and the interassay coefficient of variation was 20%.

We used an independent sample t test to test for a statistically significant difference between the mean 25(OH)D serum level among those who developed kidney stones and those who did not develop kidney stones. We also calculated a Cox regression hazard ratio at the median 25(OH)D serum level (50 ng/mL), to determine if individuals in this study with higher 25(OH)D serum levels had a higher hazard of developing kidney stones. We performed a Mann–Whitney U test, as well as a Kruskal–Wallis test, to determine if there was an association between 25(OH)D serum level and kidney stone incidence. We also applied multivariable logistic regression to determine if individuals with higher 25(OH)D serum levels were at higher risk of developing kidney stones. We assessed kidney stones as a binary variable (yes, if participant reported a kidney stone incident within the study period, and no, if not).

The predictor variable of interest was 25(OH)D serum level. We categorized serum level into roughly equal tertiles of individuals with no reported kidney stones—specifically, less than 42 ng/mL, 42 to 57 ng/mL, and 58 ng/mL or higher. Other covariates, stratified equally or by clinical relevance, included age (2 categories: younger than 55 years and 55 years or older), gender, body mass index (BMI; defined as weight in kilograms divided by the square of height in meters, with self-reported height and weight, 2 categories: <30 and ≥ 30), self-reported daily vitamin D supplement intake (3 categories: <3000 IU, 3000–5000 IU, and >5000 IU), and self-reported daily calcium supplement intake (3 categories: 0 mg, 1–500 mg, and >500 mg). We performed all statistical analyses with SPSS statistics version 20 (IBM, Armonk, NY). We conducted power analyses with G*Power version 3.1.6 (Franz Faul, University of Kiel, Kiel, Germany).

RESULTS

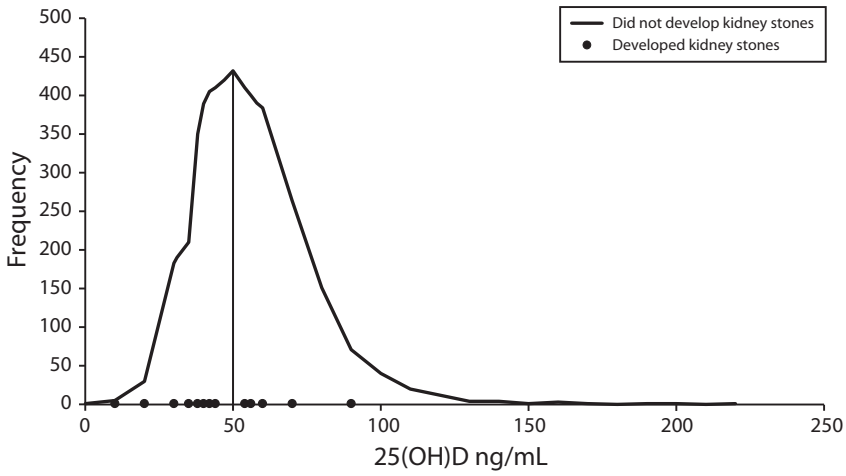
This study included 2012 participants who completed at least 2 questionnaires and provided at least 2 blood samples within the study period of December 2008 to March 2012 (40 months). Among all of the participants, 13 reported a kidney stone incident. Incidences of kidney stones occurred between January 2010 and June 2012. Participants contributed a total of 3199 person-years, with an average time of 580 days per participant. The incidence rate was 4 per 1000 person-years (3 per 1000 person-years for women and 6 per 1000 person-years for men).

This cohort had a higher proportion of female participants; however, more than half of the participants who developed kidney stones were male (Table 1). The mean 25(OH)D serum level among those who developed kidney stones was 47 ng/mL, with a median serum level of 43 ng/mL. The mean 25(OH)D serum level among those who did not develop kidney stones was 50 ng/mL, with a median of also 50 ng/mL ($t = 0.93$; $P = .35$). Among the 13 individuals who developed kidney stones, 8 were below the median serum level of 50 ng/mL, and 5 were

TABLE 1—Demographic Characteristics: GrassrootsHealth Cohort, 2009–2012

Characteristics	Developed Kidney Stones, No.(%[a]) or Mean ±SD	Did Not Develop Kidney Stones, No. (%) or Mean ±SD
Total	13 (100)	1999 (100)
25(OH)D, ng/mL	47 ±18	50 ±21
< 42	5 (39)	651 (33)
42–57	6 (46)	678 (34)
> 57	2 (15)	670 (34)
Gender		
Male	8 (62)	767 (38)
Female	5 (38)	1232 (62)
Age, y	60 ±10	53 ±14
< 55	4 (31)	1000 (50)
≥ 55	9 (69)	999 (50)
BMI*	29 ±6	25 ±5
< 30	8 (62)	1725 (86)
≥ 30	5 (38)	274 (14)
Calcium, mg/d	330 ±360	380 ±1164
0	5 (38)	918 (46)
1-500	5 (38)	585 (29)
> 500	3 (23)	422 (21)
Vitamin D intake, IU/d	4600 ±3200	4200 ±4400
< 3000	5 (38)	625 (31)
3000–5000	3 (23)	695 (35)
> 5000	5 (38)	679 (34)

Note. 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index (defined as weight in kilograms divided by the square of height in meters). The sample size was n = 2012.
[a]Percentages have been rounded and may not sum up to 100.
*$P < .05$.



Note. 25(OH)D = 25-hydroxyvitamin D. Line represents median 25(OH)D serum level of 50 ng/mL among those who did not develop kidney stones. We excluded an outlier of a participant who did not develop a kidney stone (397 ng/mL). A recommendation to consult with a physician was sent to the participant. The sample size was n = 2012.

FIGURE 1—Frequency distribution of 25(OH)D among participants who developed or did not develop kidney stones: GrassrootsHealth cohort, 2009–2012.

equal to or above it (Figure 1). Participants aged 55 years or older, male, or with a BMI of 30 or greater had a higher incidence rate of kidney stones compared with other participants. Higher 25(OH)D levels were associated with a trend toward lower incidence of kidney stones in an unadjusted analysis, although the trend was not statistically significant ($\chi^2 = 1.98$; $P = .37$).

The Cox regression hazard ratio of developing kidney stones at a 25(OH)D serum level of 50 ng/mL or higher, compared with lower than 50 ng/mL was 0.48 (95% confidence interval [CI] = 0.14, 1.67) after we adjusted for age, gender, BMI, daily vitamin D intake, and supplemental daily calcium intake. Lower 25(OH)D serum levels had higher odds of developing kidney stones, although this result was not statistically significant ($P = .42$; Table 2). Individuals with BMI of 30 or greater had more than a 3-fold higher likelihood of developing kidney stones (odds ratio = 3.5; 95% CI = 1.1, 11.3), and BMI was the only significant covariate ($P = .03$).

DISCUSSION

We did not find a statistically significant association between kidney stones and 25(OH)D serum level in the range of 20 to 100 ng/mL. This finding differed indirectly from that of the Women's Health Initiative, which found that participants assigned to 1000 milligrams per day of calcium (as calcium carbonate) and 400 international units per day of vitamin D had a slightly raised risk of self-reported kidney stones.[1]

In the present study, older age, male gender, and higher BMI were all found to be risk factors for developing kidney stones, which is consistent with findings from the Mayo Clinic.[9] As demonstrated by Garland et al.[7] any given vitamin D intake dose may result in a wide range of 25(OH)D levels, and part of that variation is attributable to BMI. Previous studies have demonstrated that individuals with high BMI need higher vitamin D intake than their leaner counterparts to achieve the same 25(OH)D serum level.[10–12] Therefore, any associations previously found with high vitamin D supplementation and increased incidence of kidney stones may be a result of BMI.

Previous studies have found a similar incidence rate in the range of about 3 per 1000 person-years.[13–16] The incidence rate in this study was slightly higher but consistent with previous findings, at 4 per 1000 person-years (95% CI = 2.2, 6.9). This study included a more general population of both men and women, compared with former studies that included only women.[17–19] The incidence rate among women in the present study was 2.6 per 1000 person years (95% CI = 0.1, 3.7), also consistent with previous findings.

Limitations and Strengths

This study had some limitations. It utilized self-reported data, and with any self-reported data some recall bias may occur. However this study had 100% adjudication, whereas the Women's Health Initiative did not.[1,20] This self-selected cohort of individuals interested in tracking their vitamin D status may be more likely to be taking doses larger than those of the general population, and also more likely to adhere to supplementation regimens. However, if vitamin D supplementation were a substantial cause of kidney stones, it might be expected that there would be more cases as supplement levels increased, which is the opposite of what was found. We did not have sufficient power to exclude a risk such as reported from the Women's Health Initiative.[1] Nevertheless, the observed trend is consistent with no association. Furthermore, low power may be inevitable because of the low annual incidence rate of kidney stones among the US population (about 0.3% to 1.0%).[13–16,21] Another limitation of the present study was the short period of follow-up, averaging approximately 1.6 years. However, this cohort will continue to be followed in coming years.

Despite the few limitations, there are several strengths of this study. This study is the first of its kind, to the authors' knowledge, to include participants with a wide range of 25(OH)D serum levels, especially on the higher end of the spectrum between 40 and 100 ng/mL, and is therefore a more rigorous test of the suggested association than the Women's Health Initiative study.[1]

The findings from this study lessen physiological concern about increasing 25(OH)D serum level to within the range of 40 to 60 ng/mL.

A recent article that alluded to an association between serum 25(OH)D concentration and risk of kidney stones simply cited the slight association that was found between assignment of participants in the Women's Health Initiative to calcium and vitamin D, compared with placebo, with incidence of self-reported kidney stones.[22,23] Because

TABLE 2—Multivariate Logistic Regression for Kidney Stones: GrassrootsHealth Cohort, 2009–2012

Factor	b (SE)	*t*	OR (95% CI)	*P*
25(OH)D, ng/mL				.42
<42 (Ref)	1.00		1.0	
42–57	0.028 (0.65)	0.002	1.0 (0.3, 3.7)	
>57	–1.07 (0.91)	1.371	0.4 (0.1, 2.1)	
Gender				.11
Male	0.95 (0.59)	2.612	2.6 (0.8, 8.2)	
Female (Ref)	1.00		1.0	
Age, y				.26
< 55 (Ref)	1.00		1.0	
≥ 55	0.71 (0.62)	1.286	2.0 (0.6, 6.9)	
BMI				.03
< 30 (Ref)	1.00		1.0	
≥ 30	1.27 (0.59)	4.610	3.5 (1.1, 11.3)	
Calcium, mg/d				.79
0 (Ref)	1.00		1.0	
1–500	0.60 (0.65)	0.847	1.8 (0.5, 6.4)	
> 500	0.39 (0.77)	0.253	1.5 (0.3, 6.6)	
Vitamin D intake, IU/d				.65
< 3000 (Ref)	1.00		1.0	
3000–5000	–0.37 (0.76)	0.233	0.7 (0.2, 3.1)	
> 5000	–0.05 (0.71)	0.005	1.0 (0.2, 3.8)	

Note. 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index (defined as weight in kilograms divided by the square of height in meters); CI = confidence interval; OR = odds ratio. The sample size was n = 2012.

calcium and vitamin D were given together in the Women's Health Initiative, it is impossible to conclude whether the slightly higher incidence of kidney stones in the calcium and vitamin D intervention group (2.5%) compared with the control group (2.1%) was attributable to vitamin D rather than the calcium carbonate used in the intervention.

Conclusions

Choice of a safe, optimal daily intake of vitamin D is a topic of considerable interest within the public health and medical community. In general, it is wisest to aim for a specified serum concentration of 25(OH)D, and determine an intake for the individual. So serum 25(OH)D, the physiological target for disease prevention,[3] should be measured whenever possible. When testing is impossible, the tolerable upper-level intakes of vitamin D specified by the National Academy of Sciences (i.e., 4000 IU per day for persons aged 9 years and older[24]) is a benchmark for consideration by physicians. A 4000 international unit intake is typically associated with a serum 25 (OH)D concentration in the 40 to 60 ng/mL range.[25,26] This range has been proposed by some investigators as safe and optimal for prevention of several important diseases that are associated with vitamin D deficiency.[25–28] ■

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Contributors

S. Nguyen wrote the article, analyzed and interpreted data, and created figures and tables. L. Baggerly assisted with the study design, data interpretation, and editing of the final article. C. French collected the data, conducted the literature search, assisted with data interpretation, and revised the article. R. P. Heaney and C. F. Garland assisted with the study design, interpreted the data, and revised the article. E. D. Gorham also assisted with the study design and data interpretation.

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Human Participant Protection

All participants have given informed consent, and this research study was approved by the Western institutional review board (Olympia, WA; WIRB study 1126093).

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