Monthly high-dose vitamin D supplementation does not increase kidney stone risk or serum calcium: results from a randomized controlled trial

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ABSTRACT

Background: A growing number of randomized controlled trials (RCTs) are investigating the potential health benefits of high-dose vitamin D supplementation. However, there are limited RCT data on the safety of calcium-related adverse effects.

Objective: We investigated the incidence of kidney stone and hypercalcemia events in a large, population-based RCT of vitamin D supplementation.

Design: The Vitamin D Assessment (ViDA) study was a randomized, double-blind, placebo-controlled trial of vitamin D supplementation in 5110 participants in Auckland, New Zealand. This trial investigated the impact of monthly 100,000 IU vitamin D_3 supplementation over several years on cardiovascular events, respiratory infections, and falls/fractures. Participants provided information about recent kidney stone events in regular questionnaires sent to them with study capsules. Hospitalization data for kidney stones were collected from health authorities. Serum calcium was measured in an 8% subsample of participants who returned annually for blood tests. HRs of time to the first kidney stone event were calculated by Cox regression.

Results: During a median follow-up of 3.3 y, 158 participants reported a kidney stone event (76 vitamin D, 82 placebo). The HR of reporting the first kidney stone event was 0.90 (95% CI: 0.66, 1.23; $P = 0.51$) for participants in the vitamin D arm compared with the placebo arm. There were 18 urolithiasis events in the hospitalization records: 7 in the vitamin D arm and 11 from the placebo arm. The HR to the first hospitalization urolithiasis event was 0.62 (95% CI: 0.24, 1.26; $P = 0.30$) in the vitamin D arm compared with the placebo arm. From the subsample annual blood test, there was no case of hypercalcemia in the vitamin D arm, compared with 1 in the placebo arm.

Conclusion: Over a median of 3.3 y, monthly supplementation with 100,000 IU vitamin D_3 did not affect the incidence rate of kidney stone events, or hypercalcemia. This study was registered at clinicaltrials.gov as ACTRN12611000402943. *Am J Clin Nutr* 2019;109:1578–1587.

Keywords: bolus dose, vitamin D supplementation, randomized controlled trial, kidney stone, hypercalcemia

Introduction

For many years, there have been concerns that vitamin D supplements could increase the risk of kidney stones and other calcium-related adverse events (1). A 2014 Cochrane review reported an increase in kidney stone events in 4 trials among participants taking vitamin D in combination with calcium (risk ratio [RR] = 1.17; 95% CI: 1.02, 1.34; $P = 0.02$) (2). In contrast, a more recent (2016) systematic review of calcium-related adverse events (hypercalcemia, hypercalciuria, and kidney stones) in randomized controlled trials (RCTs) with any dose of vitamin D_2/D_3 supplementation taken for ≥6 mo found that vitamin D did not increase the risk of nephrolithiasis (RR = 0.66; 95% CI: 0.66, 1.09; $P = 0.10$) (3). However, the latter review also found that vitamin D significantly increased the risk of hypercalcemia (RR = 1.14; 95% CI: 1.09, 2.18; $P = 0.01$) and hypercalciuria (RR = 1.64; 95% CI: 1.06, 2.53; $P = 0.03$). The hypercalcemia results of the latter review were consistent with that of another Cochrane review in postmenopausal women and older men with fractures with 17,124 participants from 21 trials (RR = 2.28; 95% CI = 1.57, 3.31; $P < 0.001$). However, studies with vitamin D analogs were also included in the latter meta-analysis (4).

In recent years, there has been an increase in the number of RCTs that have administered intermittent (bolus) doses of vitamin D supplements to determine health benefits beyond bone disease (5–8). However, the effect of bolus dosing on

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Abbreviations used: HR, hazard ratio; RCT, randomized controlled trial; RDA, Recommended Dietary Allowance; RR, risk ratio; ViDA, Vitamin D Assessment trial; 25(OH)D, 25-hydroxyvitamin D.

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calcemic adverse events, such as kidney stones, hypercalcemia, and hypercalciuria, is unclear. The small number of studies that have reported on the safety of bolus dosing found mixed results (1, 7, 9–16).

Most of the previous studies gave vitamin D for ≤2 y and had small sample sizes, limiting their ability to detect any long-term adverse calcium-related effects from vitamin D supplementation. Thus, it remains unclear whether giving vitamin D supplements by themselves in large bolus doses for periods >2 y increases the incidence of kidney stones and other calcium-related effects.

There are currently a small number of large ongoing RCTs giving long-term high-dose vitamin D supplementation (17), which have the potential to provide further evidence on the safety of vitamin D. One of these is the Vitamin D Assessment (ViDA) study, which randomized 5108 participants and gave a monthly bolus vitamin D_3 dose of 100,000 IU for a median duration of 3.3 y (18). This RCT provides an opportunity to evaluate the safety of long-term vitamin D bolus dosing in the general population. The aim of this report is to investigate if 100,000 IU vitamin D_3/mo taken for ≥3 y increases risk of kidney stones and hypercalcemia compared with placebo.

Methods

The ViDA study methods have been reported in previous publications (18, 19). Briefly, the ViDA study was a double-blind RCT of monthly vitamin D supplementation to investigate the primary outcome of cardiovascular events (19). Secondary outcomes were respiratory infections, falls, and fractures (20). The ViDA study pre-declared in the safety section (2.10) of its methods manuscript that kidney stone events (self-reports and hospitalization) and serum calcium would be evaluated (18), as specified in the study protocol (19 [online supplementary file, page 23]).

The study was carried out in Auckland, New Zealand, approved by the Multi-Region Ethic Committee, Wellington (MEC/09/09/082), and registered with the Australian and New Zealand registry for clinical trials with a trial number of ACTRN12611000402943 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=ACTRN12611000402943). All participants gave written consent. In summary, participants were recruited mainly from family physician registers and some from community groups. Participants were included if they were aged 50–84 y, living in Auckland with the continued expectation to live there for 3–4 y of the study period. They were excluded for the following reasons: *1*) if they were taking vitamin D supplement >600 IU/d for those aged 50–70 y and >800 IU for those aged 71–84 y; *2*) if they were involved in any other study; *3*) if they had a baseline serum calcium level of >2.5 mmol/L; or *4*) if they had a history of parathyroid disease, hypercalcemia, sarcoidosis, nephrolithiasis, gastric bypass surgery, or psychiatric disorders that would interfere with their participation.

Baseline assessment and randomization

All participants came to the University of Auckland clinic for their baseline assessment, where they were asked about their socioeconomic and demographic status (age, sex, ethnicity, country of birth, marital status, occupation, hours at work), lifestyle factors (smoking, alcohol consumption, physical activities during a week, sun exposure, and screen time/television watching hours), medical history (including history of prescription medication and supplement intake), and quality of life. Anthropometric measurements for height (nearest 0.1 cm) and weight (nearest 0.1 kg) in light clothing without shoes were also taken. A nonfasting blood sample was collected to immediately measure serum calcium (an exclusion criterion),which was performed with an Advia 2400 analyzer (Siemens Healthcare Diagnostics), and aliquots were stored at –80°C for later measurement of 25-hydroxyvitamin D (25[OH]D) by liquid chromatography–tandem mass spectrometry (ABSciex API 4000).

Immediately after the baseline assessment, a run-in blinded placebo capsule, along with a questionnaire, was sent to each person's home with a reply-paid envelope. Those who returned the questionnaire and stated that they took their capsule and their serum calcium level was ≤2.50 mmol/L were eligible for the study. We used a block randomization method to allocate participants to either the vitamin D or placebo arm stratified by ethnicity and age. Both participants and staff were blinded to the study capsule allocation. The number of people excluded (with reasons) is shown in **Figure 1**.

Vitamin D intervention

Identical-looking soft-gel oral capsules containing sunflower oil, either with or without 100,000 IU vitamin D_3, were sourced from Tishcon Cooperation. Participants were given 2 capsules for the first month, starting individually during June 2011–January 2013. Thereafter, from the second month after randomization, participants were given 1 capsule/mo. The capsules were mailed monthly to participants' homes up to June 2013, and from July 2013, for cost reasons, 4 capsules were mailed every 4 mo (with monthly reminders to take the capsule sent by email or letter).

Outcomes

Self-reports of kidney stones.

A questionnaire (with a reply-paid envelope and the study capsule) was also sent monthly from June 2011 until November 2013, and then every 4 mo from March 2014 until July 2015 when follow-up ended. This questionnaire asked participants about their adherence to taking the study capsule and any adverse effects attributed to the capsule by the participant. For kidney stones, participants were also asked: "Since you took your last capsule (about one month ago) have you been diagnosed by a doctor as suffering from any of the following conditions?," one of which was "Kidney stones", with "Yes/No" response options. In the 4-monthly questionnaire, the same question was asked about kidney stones over the last 4 mo, along with the number of times (if at all) the participant was admitted to hospital.

Hospitalization for kidney stones.

All New Zealand residents are allocated a unique National Health Index (NHI) number by the Ministry of Health, which was collected at the baseline assessment and used to link study participants to any hospitalizations for urolithiasis (ICD-10 codes N20–N23) in the Ministry of Health database from randomization to 31 July 2015.

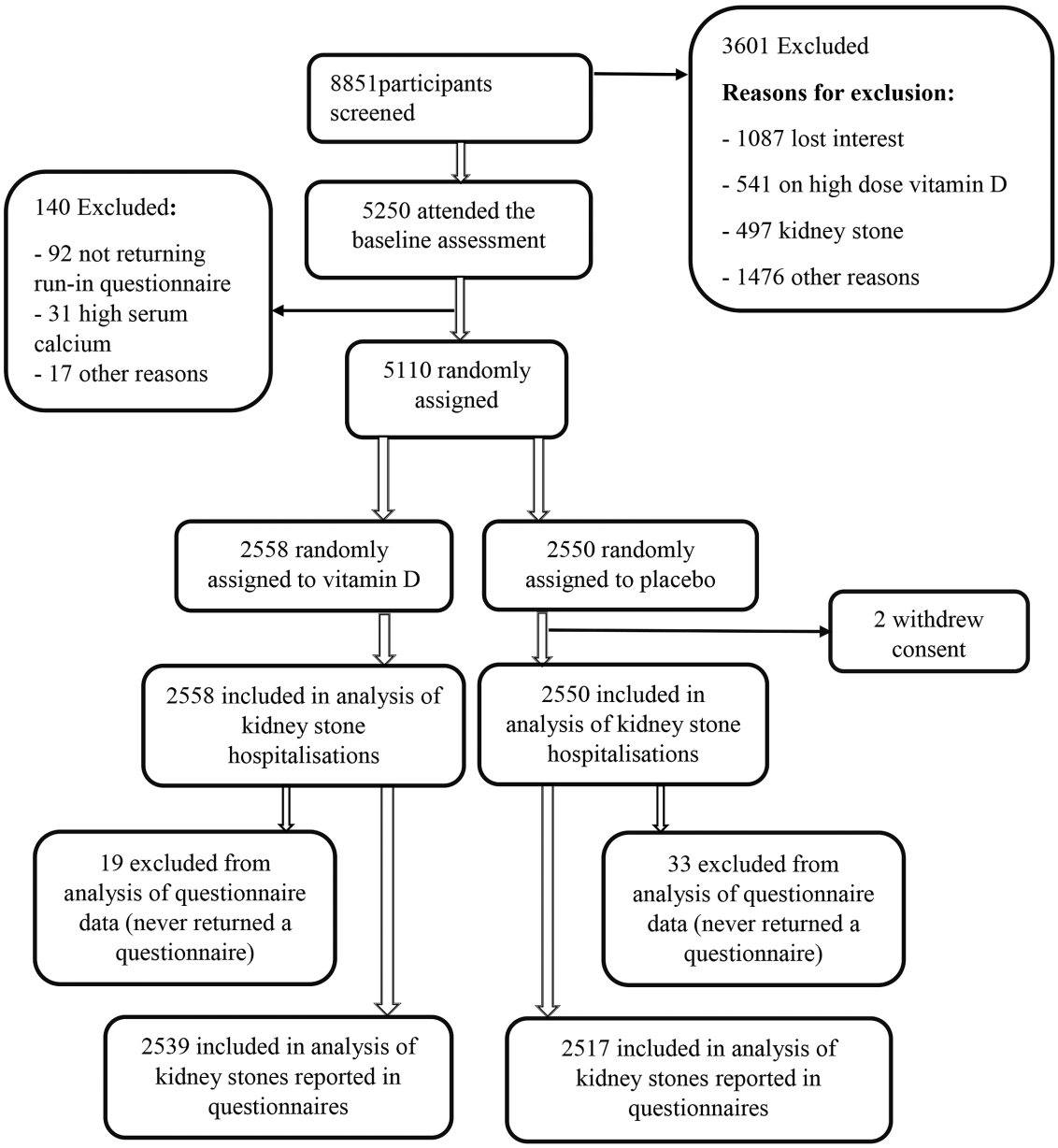

FIGURE 1 Flow diagram of ViDA study participants included for the kidney stone outcome.

Blood samples.

A 10% randomly selected sample of participants was invited to attend follow-up clinic visits at 6 mo, 1 y, 2 y, and 3 y after their baseline assessment to collect a nonfasting blood sample; 438 (85%) of 515 participants agreed. Serum calcium (corrected) was measured immediately after collection and frozen aliquots were measured for 25(OH)D levels by the previously reported methods.

Statistical analysis.

All statistical analyses were done with SAS version 9.4. HRs for time to the first event were calculated by Cox regression models for survival analysis. Time-dependent repeated events were calculated through the use of the mean cumulative function. For kidney stone events reported in the home questionnaire, the date of the event was defined as approximately halfway through the coverage period of the questionnaire. If a questionnaire was not returned, it was assumed no event happened during the period of the questionnaire if the participant returned a subsequent questionnaire. Participants who never returned a questionnaire were excluded from data analysis. Participants were censored (i.e., last date noted for estimation of follow-up time) at the last questionnaire they returned. All models were adjusted for age, sex and ethnicity. A subgroup analysis for those with a baseline 25(OH)D <75 nmol/L compared with ≥ 75 nmol/L was performed. We chose this level as it has previously been considered an optimal serum concentration for different health

TABLE 1 Baseline characteristics of study participants[1]

Variable	Vitamin D, $n = 2558$	Placebo, $n = 2550$
Age, y		
Mean ± SD	65.9 ± 8.3	65.9 ± 8.3
Range	50.0–84.0	50.0–84.0
Sex		
Female	1046 (40.9)	1093 (42.9)
Male	1512 (59.1)	1457 (57.1)
Ethnicity group		
European/other	2127 (83.2)	2126 (83.4)
Māori	137 (5.4)	135 (5.3)
Pacific	168 (6.6)	166 (6.5)
South Asian	126 (4.9)	123 (4.8)
BMI, kg/m^2		
Normal	609 (23.8)	573 (22.5)
Overweight	1145 (44.8)	1149 (45.1)
Obese	782 (30.6)	801 (31.4)
Deseasonalized 25(OH)D, nmol/L		
Mean ± SD	61.9 (23.8)	61.6 (23.7)
Deseasonalized 25(OH)D, nmol/L		
≥75	839 (32.8)	840 (32.9)
<75	1719 (67.2)	1710 (67.1)
Baseline calcium, mmol/L		
Mean ± SD	2.28 ± 0.07	2.28 ± 0.11
Currently on vitamin D/minerals		
Vitamin D	208 (8.0)	200 (7.8)
Calcium	125 (5.0)	127 (5.0)
Vitamin D intake (categories by amount), IU		
None/dose unknown	2351 (93.2)	2351 (93.1)
<200	103 (4.1)	104 (4.1)
200–400	44 (1.7)	47 (1.9)
>400–800	25 (1.0)	22 (0.9)

[1]Numbers are frequency (column percentage), unless otherwise stated.

outcomes (21, 22). We aimed to determine whether vitamin D supplementation increased the risk of kidney stone events in participants with a baseline level of 25(OH)D above this higher level as compared to those with a lower baseline.

Incidence RRs for reporting a kidney stone event when pooling monthly and 4-monthly questionnaires based on total number of events per participant were calculated with the use of a negative binomial regression model adjusted for age, sex, and ethnicity. Mixed models were used for the analysis of repeated serum calcium measurements. Linear regression analysis was run to see if a change in serum 25(OH)D from baseline to year 3 was associated with a change in serum calcium concentrations for the same period.

Results

Figure 1 shows the flow diagram of randomized participants. A total of 8851 people were screened for entry into the study, 5250 had baseline assessments, of whom 5110 were randomized. Two participants subsequently withdrew, leaving 5108 participants in the study: 2558 in the vitamin D arm and 2550 in the placebo arm.

Analysis of the self-reported kidney stones from the home questionnaire was restricted to the 5056 participants (99%) who returned ≥1 questionnaire. Analysis of the hospitalization data from the Ministry of Health was on an intention-to-treat basis as these data were available for all 5108 participants. The mean ± SD age of participants was 65.9 ± 8.3 y. The baseline characteristics of participants are shown in **Table 1**. Retention was high, with 86% and 85% active participants in the vitamin D and placebo arms, respectively, returning the penultimate or final home questionnaires. By the end of follow-up (31 July 2015), 65 participants in the vitamin D arm and 58 in the placebo arm had died.

Figure 2 shows change of 25(OH)D from baseline to year 3, by treatment arms. Results of serum 25(OH)D for the subsample with 333 people at year 3 showed a significant increase in the vitamin D arm from a mean baseline of 62 ± 24 nmol/L to 135 ± 40 nmol/L at year 3 (mean difference = 71 ± 42 nmol/L; $P < 0.001$), which was significantly higher than that of participants in the placebo arm, changing from 62 ± 23 nmol/L at baseline to 66 ± 23 nmol/L at year 3 (mean difference = –2 ± 22 nmol/L; $P = 0.35$). The mean difference between vitamin D and placebo arms at year 3 was 69.4 ± 35.0 nmol/L ($P < 0.001$).

Kidney stone events reported in questionnaires

Overall, 200 kidney stone events were reported by 158 participants in the monthly and 4-monthly questionnaires, of which 42 were recurrent/repeated events. The proportions of participants reporting a kidney stone event in the monthly and 4-monthly questionnaires are shown in **Table 2**, along with

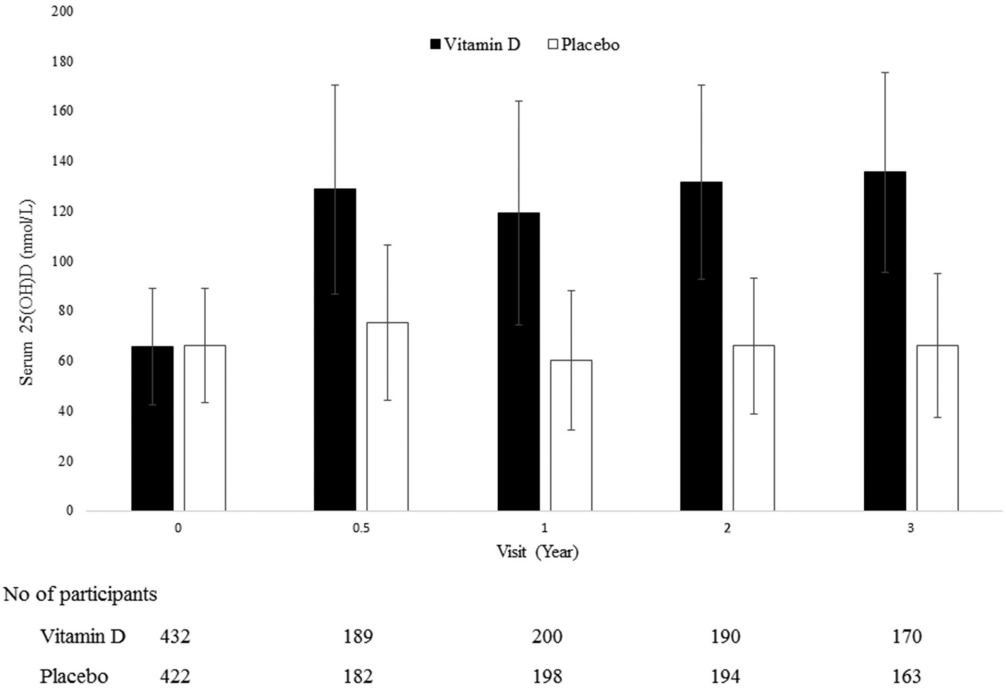

FIGURE 2 Mean ± SD serum 25(OH)D from baseline to year 3, in subsample, by treatment arm. 25(OH)D, 25-hydroxyvitamin D.

HRs of time to first event, adjusted for age, sex, and ethnicity. For both questionnaires combined, 3.0% of participants in the vitamin D group and 3.3% in the placebo group reported a kidney stone event (HR: 0.90; 95% CI: 0.66, 1.23; $P = 0.51$) (**Figure 3**). A higher proportion of kidney stone events was reported for the monthly questionnaire (vitamin D 2.0%, placebo 2.4%) than for the 4-monthly questionnaire (vitamin D 1.0%, placebo 0.8%). When participants were categorized by baseline 25(OH)D concentration as those with 25(OH)D <75 nmol/l compared with ≥75 nmol/l, the HRs were not increased in either subgroup, indicating that vitamin D supplements did not increase the risk of kidney stones even in people with higher vitamin D concentrations (Table 2).

Table 3 shows the full multivariable model for HRs of reporting a kidney stone event in vitamin D compared with placebo arm plus covariates. Of the latter, only gender explained variations in kidney stone events reported in questionnaires, with men slightly more likely to report a kidney stone event than women (HR: 1.02; 95% CI: 1.01, 1.04; $P = 0.03$). There was no statistically significant difference between age groups ($P = 0.27$) (Table 3).

Only 17 out of 710 (2.4%) of participants who were taking vitamin D or calcium supplements at baseline reported a kidney stone event. Of these, 4 out of 252 (1.5%) who were taking calcium supplements reported a kidney stone event; 1 in the vitamin D and 3 in the placebo arm. These numbers were too small to compare the treatment arms.

For recurrent kidney stone events, there was no difference in time to first/recurrent events after adjustment for age, sex, and ethnicity (HR: 0.96; 95% CI: 0.66, 1.41; $P = 0.85$). Repeated events were further analyzed by calculating incidence rate ratios of kidney stones. The incidence rate of reporting an adverse event in the combined monthly/4-monthly questionnaires was 1.07 (95% CI: 0.87, 1.31) and 1.11 (95% CI: 0.90, 1.35) per 1000

TABLE 2 Proportion of participants during follow-up who reported kidney stone events or were hospitalized for urolithiasis, and HRs of time to first event for vitamin D compared with placebo (reference)[1]

	Vitamin D, *n* (%)	Placebo, *n* (%)	[1]HR (95% CI)	*P* value (Wald χ^2)
Questionnaires				
All: monthly and 4-monthly	76/2539 (3.0%)	82/2517 (3.3%)	0.90 (0.66, 1.23)	0.51
Monthly	52/2539 (2.0%)	62/2517 (2.4%)	0.82 (0.57, 1.18)	0.29
Four-monthly	24/2539 (1.0%)	20/2517 (0.8%)	1.17 (0.65, 2.11)	0.60
Baseline serum 25(OH)D, nmol/L				
<75	54/1704 (3.2%)	51/1608 (3.0%)	1.03 (0.70, 1.51)	0.86
≥75	22/835 (2.6%)	31/837 (3.7%)	0.70 (0.40, 1.20)	0.19
Hospitalizations (ICD10: N20–23)	7/2558 (0.3%)	11/2550 (0.4%)	0.62 (0.24, 1.26)	0.30

[1]Cox regression analysis was used to estimate the HRs, adjusted for age, sex, and ethnicity.

person-months in the vitamin D and placebo arms, respectively. Comparing the rates in the vitamin D and placebo arms with the use of binomial regression, adjusted for age, sex, and ethnicity, yielded an incidence RR of 0.95 (95% CI: 0.72,1.26; $P = 0.73$).

Hospitalizations for urolithiasis

There were 25 hospitalization events for urolithiasis (8 in the vitamin D arm and 17 in the placebo arm), some of which were recurrent for the same individual. These occurred in 18 participants (7 in the vitamin D arm and 11 in the placebo arm). Of these, 3 and 5 participants had a kidney stone diagnosis, in the vitamin D and placebo arms, respectively. The HR of time to first urolithiasis event was not increased in the vitamin D arm compared with placebo (HR: 0.62; 95% CI: 0.24, 1.26; $P = 0.30$) (Table 2).

Hypercalcemia

Figure 4 shows the mean ± SD adjusted serum calcium levels for participants in the random subsample who returned regularly for repeated blood tests. There was no significant difference between arms in serum calcium levels at baseline, 6 mo, 12 mo, 24 mo, and 36 mo ($P > 0.05$). An increasing trend from a mean of 2.28 mg/dL at baseline to 2.36 mg/dL at year 3 was seen in both arms (Figure 4). Multivariable analysis of repeated measurements did not show a significant difference in time × treatment effect ($\beta = 0.005$; SE = 0.003; $P = 0.14$).

Only one participant had hypercalcemia above the threshold of >2.6 mg/dL, which was at year 3. This person was referred to an endocrinologist who was blind to the participant's allocation status, and who diagnosed primary hyperparathyroidism and recommended that the participant continue to take the study medication. This person, at the end of the study, was revealed to be in the placebo arm. No participant in the vitamin D arm of the randomly selected subgroup developed hypercalcemia.

Figure 5 shows changes in serum calcium from baseline to year 3 in relation to changes in serum 25(OH)D, by treatment arm (adjusted for age, sex, and ethnicity). Testing changes from baseline to year 3 in both variables showed that changes in serum 25(OH)D were not associated with changes in serum calcium levels ($\beta = 0.03$; SE = 0.01; $P = 0.65$) (Figure 5).

Discussion

Analyses of the ViDA study showed that a bolus dose of 100,000 IU vitamin D_3 per month for a median period of 3.3 y, and up to a maximum of 4.2 y, did not increase the incidence of kidney stones in adults aged 50–84 y. Nor did it result in any cases of hypercalcemia among those with follow-up serum calcium measurements, with the only case of hypercalcemia being detected in the placebo group. These findings are consistent with those of previous smaller clinical trials that have used bolus doses (10, 15, 23–26), none of which found hypercalcemia and kidney stone events associated with vitamin D supplementation. The Cochrane review study that found an increased risk of kidney stone events included studies that had also given calcium in combination with vitamin D to the treatment arm (2). Our study, with its larger sample size and longer follow-up period, extends

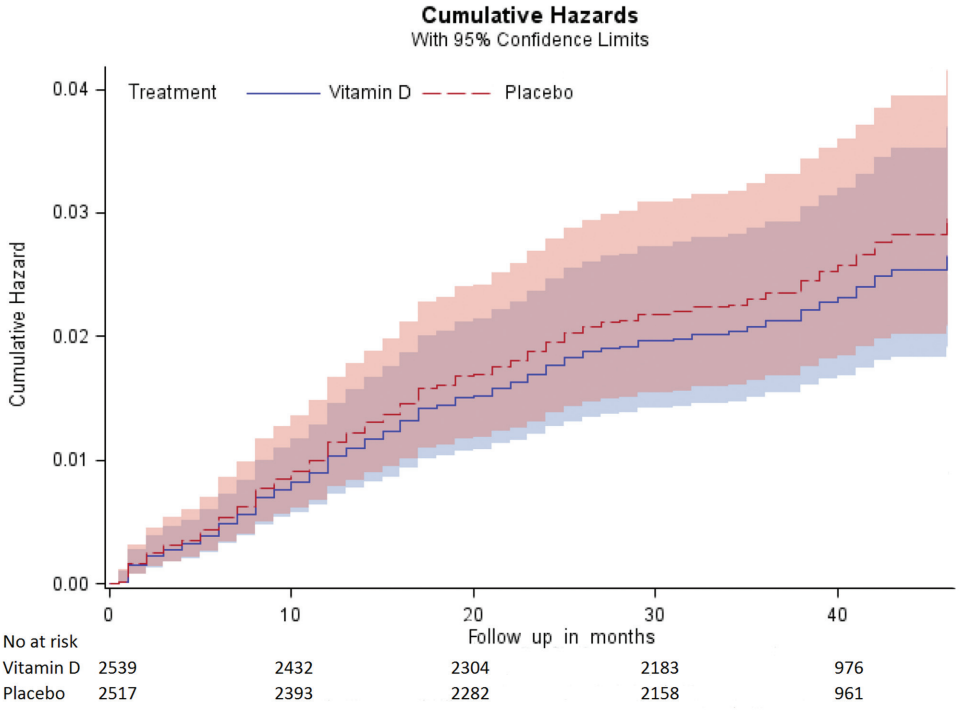

FIGURE 3 Cumulative HR to first kidney stone event reported in questionnaires, by treatment arm.

TABLE 3 Hazard ratio of vitamin D supplementation on self-reported kidney stone events (first event)[1]

Parameter		*n* (%)	HR	95% Wald robust CI	*P* value
Treatment	Vitamin D	2539 (50.2)	0.9	0.66, 1.23	0.51
	Placebo	2517 (49.8)	ref	—	
Sex	Male	2935 (58.1)	1.45	1.04. 2.03	0.03
	Female	2121 (41.9)	ref	—	
Ethnicity	Māori	261 (5.2)	1.82	0.98, 3.40	0.16
	Pacific	318 (6.3)	1.59	0.84, 3.00	
	South Asian	248 (4.9)	1.13	0.52, 2.44	
	European/other	4229 (83.6)	ref	—	
Age category, y					
	50–60	1112 (22.0)	ref	—	
	60–70	2208 (43.7)	1.26	0.81, 1.97	0.27
	70–85	1736 (34.3)	1.45	0.92, 2.30	

[1]The Cox regression model was used to estimate the HR of reporting a kidney stone event.

this previous research by showing that the null effect on kidney stone risk from vitamin D supplementation, for a period of up to 4 y, is unlikely to be due to a type 2 error. These results complement our recent findings for self-reported noncalcemic adverse events from an open-ended question recording any side-effect attributed to the study capsule by the participant, in which we found the HR of time to first event was 1.03 (95% CI: 0.90, 1.18) in the vitamin D arm compared with placebo (27).

The Institute of Medicine, when it published its vitamin D report in 2011, recommended an upper level of 4000 IU vitamin D/d intake for adults and discouraged supplementation that increases serum 25(OH)D level beyond 125–150 nmol/L, because there were few studies at that time to assess the safety of giving large doses of vitamin D for >1 y (28). The ViDA study partly fills this gap by showing that a bolus dose of vitamin D, which is equivalent of 3300 IU/d, and increased serum 25(OH)D levels up to a mean of 135 nmol/L, and a maximum of 289 nmol/L, did not result in any adverse effects on kidney stones and hypercalcemia. Furthermore, subgroup analyses by baseline 25(OH)D status showed that the HR for reporting kidney stone events was not increased for vitamin D compared with placebo in participants with baseline 25(OH)D levels either below or above 75 nmol/L (Table 2). This indicates that having a high baseline 25(OH)D level did not increase the reporting of kidney stone events with vitamin D supplementation. This is consistent with results of a recent systematic review of the effect of vitamin D supplementation for ≥6 mo on kidney stone events in 9 studies with 9619 participants, although the cut-point for

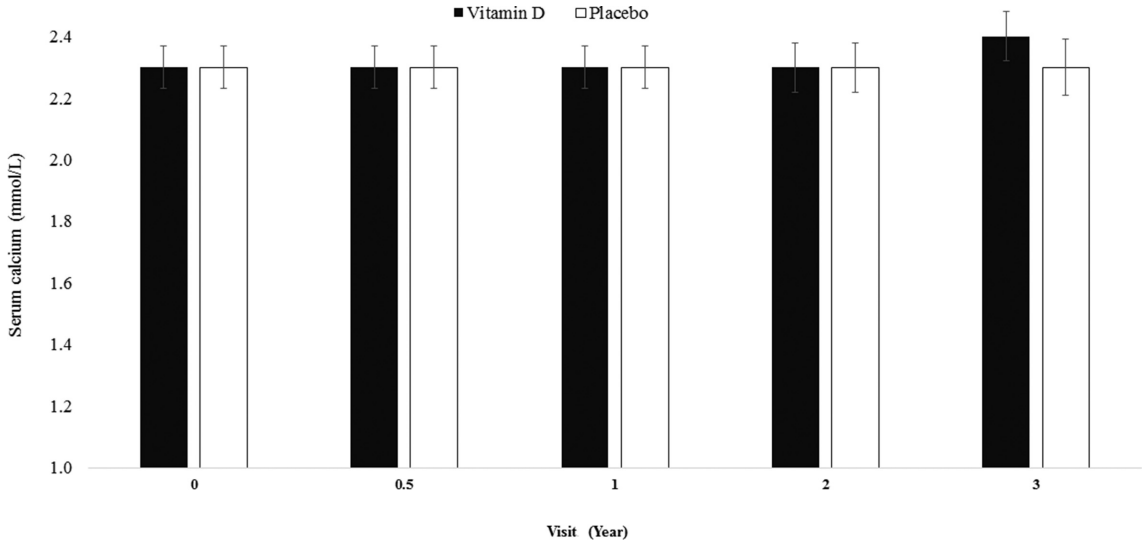

FIGURE 4 Mean ± SD serum calcium level from baseline to year 3, in subsample, by treatment arm.

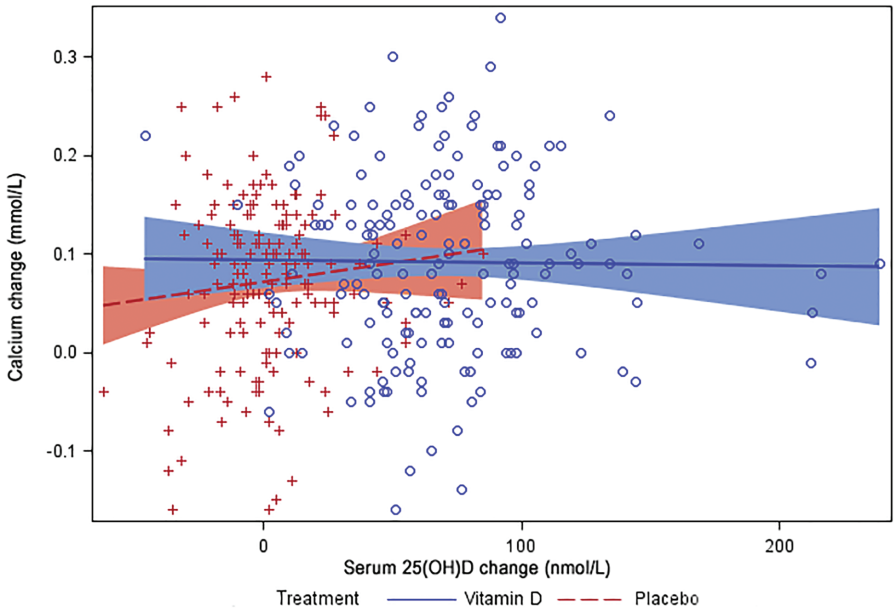

FIGURE 5 Change in serum calcium from baseline to year 3 against change in serum 25(OH)D in subsample, by treatment arm (linear regression line and 95% CI). 25(OH)D, 25-hydroxyvitamin D.

high baseline 25(OH)D levels was 50 nmol/L (3). Our results are also consistent with a review that concluded that toxicity, as measured by hypercalcemia (serum calcium >2.7 mmol/L), does not occur below serum 25(OH)D levels of 700 nmol/L (29).

Our findings for the associations between demographic variables and risk of kidney stone events are consistent with previous research. Consistent with our findings, a higher nephrolithiasis incidence in men than women has been observed in the United States (30), and also in recent New Zealand studies (31,32). The incidence also increased with age, although the evidence for increasing incidence with age is not consistent across all populations (33). With regard to ethnicity, the above Auckland study reported that Europeans and Pacific Islanders had higher kidney stone incidences than Māori and Asians (34). In addition, another study in Auckland on the temporal trend of acute nephrolithiasis found the highest incidence rates in Middle Eastern with 142/100,000, followed by Europeans with 131/100,000, and then Pacific and Māori (131 and 89 per 100,000, respectively) (34). We did not find a significant difference between ethnicities in the risk of kidney stone incidence.

We did not find a correlation between mean 25(OH)D and serum calcium concentrations at year 3 of the study, which indicates that despite a significant increase in 25(OH)D to a median of 135 nmol/L, serum calcium concentrations did not increase in the vitamin D arm with the high dose. In a similar study on obese subjects, vitamin D_3 at 1000, 5000, and 10,000 IU/d was given to patients for 21 wk to measure serum 25(OH)D response. Despite a steady increase in serum 25(OH)D concentrations by the 21st week to mean concentrations as high as 102, 154, and 186 nmol/L, respectively, serum calcium levels did not change in any of the 3 study arms (35). In agreement with the latter study, in a risk-assessment study of vitamin D supplementation in 22 RCTs with weekly, monthly, or daily doses equivalent to 1800 IU D_2 or D_3, serum calcium concentrations did not increase in response to higher doses of vitamin D supplements (36). However, most of the included studies were short term. The ViDA study did not find an increased serum calcium concentration in the vitamin D arm compared to placebo in the 8% subsample (Figure 4), which supports the safety of the applied dose over several years for this outcome.

Strengths and limitations

The major strengths of the ViDA study include its long-term follow-up (≤4 y), high adherence, high retention, and large sample size compared with previous studies that gave bolus dosing. However, despite its large size, post-hoc calculations with OpenEpi (http://www.openepi.com/Power/PowerRCT.htm), based on the proportion of placebo participants who reported a kidney stone event (3.3%), show that the study had 80% power to only detect an increased RR of 1.5 (with 2-sided 95% confidence). It is therefore possible that we failed to detect a smaller increase in kidney stones from vitamin D supplementation. However, the consistency in the findings from the questionnaire and the Ministry of Health hospitalization data supports the validity of our kidney stone findings.

There are some other potential limitations. We used a questionnaire to collect self-reported kidney stone events which is not as accurate as ultrasound. This may have caused errors in both the reporting of actual events and their timing. However, this approach has been used to measure the occurrence of kidney stones in previous major US studies (37). In addition, we used hospitalization data for urolithiasis which likely underestimated total events as not all kidney stone events result in hospitalization.

Further, we could not measure the urinary calcium to creatinine ratio in all participants, and follow-up serum calcium was only measured in ~8% of the study, so it is likely that we did not identify other cases of hypercalcemia. Nevertheless, the lack

of any hypercalcemia cases in the subsample vitamin D arm suggests that this outcome would have been very rare. Lastly, we excluded people with a history of kidney stones and it is possible our findings do not apply to them.

Conclusions

Monthly supplementation with 100,000 IU vitamin D_3 capsules was not associated with an increase in the incidence of kidney stone events or hypercalcemia compared with placebo in adults aged 50–84 y over a median follow-up of 3.3 y. The results of this study confirm the safety of 100,000 IU monthly vitamin D supplementation, equivalent to 3300 IU/d and within the 4000 IU/d dose recommended as the tolerable upper limit by the Institute of Medicine.

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