



# Safety of calcium and vitamin D supplements, a randomized controlled trial

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## Abstract

**Objective:** It is anticipated that an intake of vitamin D found acceptable by Endocrine Society Guidelines (10 000 IU/day) with co-administered calcium supplements may result in frequent hypercalciuria and hypercalcaemia. This combination may be associated with kidney stones. The objective of this study was to compare the episodes of hypercalciuria and hypercalcaemia from calcium supplements co-administered with 10 000 IU or 600 IU vitamin D daily. This design allows a comparison of the Institute of Medicine recommendation for the RDA of vitamin D along with the upper limit of calcium intake with the high intake of vitamin D suggested by the Endocrine Society.

**Context:** Harms of currently recommended high intake of vitamin D have not been studied.

**Design:** The design was a randomized controlled trial with 2 groups with evaluation every 3 months for one year: (a) CaCO<sub>3</sub> 1200 mg/day with 10 000 IU vitamin D<sub>3</sub>/day or (b) CaCO<sub>3</sub> 1200 mg/day with 600 IU vitamin D<sub>3</sub>/day.

**Patients:** This study was conducted in an ambulatory research centre in healthy, white postmenopausal women.

**Measurements:** Serum and 24-hour urine calcium were measured.

**Results:** Hypercalcaemia and hypercalciuria occurred in both groups. At the final visit, 19/48 in the high dose D group had hypercalciuria. The odds of developing hypercalciuria were 3.6 [OR = 3.6(1.39, 9.3)] times higher in the high dose D group. The odds of developing hypercalcaemia did not differ between groups.

**Conclusions:** The safe upper level of vitamin D recommended by the Endocrine Society when accompanied by calcium supplements results in frequent hypercalciuria. The risk of kidney stones at these levels should be investigated.

## KEYWORDS

calcium, hypercalcaemia, hypercalciuria, kidney stones, PTH, vitamin D

## 1 | INTRODUCTION

Dietary reference intakes (DRI) are based on a risk-management assessment model which balances benefits and harms.<sup>1</sup> The RDA

(Recommended Dietary Allowance) is the intake where 97.5% of the population is sufficient, and the tolerable upper intake level (UL) is the intake that should not be exceeded because of the likelihood of harm. The 2011 Institute of Medicine (IOM) report on calcium and vitamin D sets the adult UL for calcium at 2,000 mg/day for those 51 + years and for vitamin D for adults at 4000 IU/

day.<sup>2,3</sup> The report considered calcium along with vitamin D because of their interaction: the canonical action of vitamin D is to increase intestinal absorption of calcium. The Endocrine Society Guideline on vitamin D which followed the IOM report argued for an UL of 10 000 IU/day for vitamin D based on the risk of hypercalcaemia.<sup>4-6</sup> They stated that this intake does not cause hypercalciuria; however, the paper they cited in support of this did not report on urinary calcium excretion.<sup>6</sup>

There has been prolific research activity concerning the health benefits of calcium and vitamin D in the last two decades and many meta-analyses about their benefits.<sup>7-11</sup> There have not been as many studies of the possible harms of excessive intakes of these nutrients. Rather, harms data have usually been collected from adverse events in trials with a beneficial outcome as their primary aim. Many older trials did not even collect adverse events. Since the primary outcomes were unrelated to the harms, data on variables such as serum and urinary calcium were often not collected or presented.

In the past, consideration of harms of calcium and vitamin D was limited to acute toxicity. Excess calcium intake has been associated with hypercalcaemic crisis and renal failure.<sup>12,13</sup> This was more common in the past when milk and  $\text{CaCO}_3$  were used to treat peptic ulcer disease (milk-alkali syndrome). Similarly, vitamin D intoxication has been described with marked hypercalcaemia, hyperphosphatemia and renal insufficiency, usually from accidental poisoning.<sup>14,15</sup>

The widespread use of calcium and vitamin D supplements with the goal of prevention of chronic disease led us to consider less drastic harm than is seen in acute toxicity. An association with kidney stones has been found with calcium supplements with vitamin D but not from increased dietary calcium.<sup>16-19</sup> Some studies have reported hypercalcaemia and hypercalciuria in association with calcium/vitamin D supplements which may be the aetiology of the increase in kidney stones.<sup>12,20-25</sup> Here, we report on a study whose primary outcome is hypercalciuria/hypercalcaemia in response to calcium intake at its UL for those 51 + years with vitamin D intake either at the adult RDA (600-800 IU/day) or at the UL suggested by the Endocrine Society Guidelines (10 000 IU/day).

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

The study was a randomized, double-blind, clinical trial of one year's duration. Participants were recruited from Winthrop University Hospital employees and direct mail in the community. The investigators screened a total of 271 white postmenopausal women aged 50 and older. A total of 132 subjects who were eligible and consented to participation were randomized into one of the two study groups: (a) 10 000 IU/day vitamin D<sub>3</sub> plus 2000 mg/day calcium [(600 mg/day calcium carbonate twice a day with meals), assuming 800 mg of average intake from diet] or (b) 600 IU/day vitamin D<sub>3</sub> (assuming 200 IU/day from diet) plus 2000 mg/day calcium (1200 mg/day calcium supplement), assuming 800 mg of average intake from diet.

Inclusion criteria included serum 25(OH)D level <32 ng/mL, willingness to discontinue self-administration of vitamin D and calcium supplements, last menstrual period (LMP) greater than five years ago, and if present, hypertension and diabetes stable for the last three months. Exclusion criteria included T-score of the total hip below -2.5 standard deviations; history of osteoporotic fracture, hypercalciuria, hypercalcaemia or nephrolithiasis; hypercalciuria or hypercalcaemia at screening visit; use of medication that influences calcium or vitamin D metabolism and significant deviation from normal in medical history, physical examination or laboratory tests as evaluated by the primary investigator.

The study consisted of six visits, the first two visits being a screening/baseline and a randomization visit, followed by four more visits spaced at 3-month intervals. If subjects were eligible based on their screening and randomization visits, they were randomized into one of the two study groups. Subjects were asked to refrain from taking calcium and vitamin D supplements. Markers of calcium homeostasis [serum calcium, 24-hour urinary calcium, PTH, vitamin D metabolites and bone turnover [serum C-telopeptide (CTX)] were assessed at baseline and at each marker three-month interval. Unused medications were counted at follow-up visits.

Development of hypercalcaemia and hypercalciuria at the 3-, 6-, 9- and 12-month follow-up visits was routinely monitored. Participants with hypercalciuria or hypercalcaemia first had their laboratories repeated. If repeated levels confirmed these results, the calcium supplement was decreased to 600 mg per day. If laboratory values were still high at the next follow-up visit, the calcium supplement was discontinued completely. If the levels on the subsequent follow-up visit still showed hypercalciuria or hypercalcaemia, the vitamin D supplement was discontinued. The study was approved by the Winthrop University Hospital IRB. It was registered at ClinicalTrials.gov Identifier # NCT02019381.

### 2.2 | Laboratory methods

Serum and urine calcium were measured on the ADVIA 2400 Chemistry System. Serum parathyroid hormone (PTH) was measured with the Immulite 2000 Analyzer for the quantitative measurement of intact PTH (Diagnostic Products Corporation, Los Angeles, CA). Serum CTX was measured with a Serum Crosslaps ELISA kit made by Nordic Bioscience Diagnostics.

During the conduct of the study, serum 25(OH)D was measured by Labcorp Corporation (Burlington, NC). The immunochemiluminometric assay was performed on a DiaSorin platform. Serum samples were also analysed for vitamin D metabolites by the Department of Laboratory Medicine at the University of Washington (Seattle, WA, USA) using calibrators and controls (400  $\mu\text{L}$ ) that were spiked with deuterated internal standards. Analytes enriched during immunoaffinity purification and analysed by liquid chromatography-tandem mass spectrometry include 25(OH)D<sub>2</sub>, 25(OH)D<sub>3</sub>, 24,25(OH)<sub>2</sub>D<sub>3</sub>, 1,25(OH)<sub>2</sub>D<sub>2</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub>. Concentrations of 25(OH)D<sub>2</sub>, 25(OH)D<sub>3</sub> and 24,25(OH)<sub>2</sub>D<sub>3</sub> were standardized to NIST SRM 972a [PMID: 27091017, 22141317].<sup>26</sup> These measurements were made on stored

serum at baseline and final visits as well as visits marked by either hypercalcaemia or hypercalciuria. Samples were run concurrently. The % CV by these assays in the specific ranges are as follows: 1,25(OH)<sub>2</sub>D<sub>3</sub>: 7.95%-10.40% CV at 18.1-47.8 pg/mL; 25(OH)D<sub>3</sub>: 3.54%-4.41%CV at 9.5-32.3 ng/mL; 24,25(OH)<sub>2</sub>D<sub>3</sub>: 5.17%-7.42% CV at 1.3-4.6 ng/mL.

The vitamin D supplements were produced by Tischcon Corporation (Westbury, NY, USA) with a 20% overage to maintain shelf life (USP recommendation). Assay of supplements at the beginning of the study was 710 IU and 12 069 IU by Tischcon. Independent analysis by Covance Laboratories (Madison, WI, USA) was 755 IU and 12 700 IU, respectively.

## 2.3 | Statistical analysis

A repeated-measure mixed-effects logistic regression model was used for power analyses. A simulation study was conducted with 1000 data sets to detect an odds ratio of 1.5 for the treatment × time interaction assuming intraclass correlation coefficient (ICC) of 0.5. Type I error of 0.05 was used for all simulations. It was found that 120 patients assuming a 20% dropout would provide sufficient power (>80%) to test the binary outcome of hypercalciuria. However, a higher attrition rate (30%) than the initial assumption was estimated after a mid-study evaluation. Therefore, the sample size was adjusted accordingly. We enrolled 132 patients (66 per group), which provided sufficient (>80%) power to test our primary hypothesis.

Block randomization was performed at baseline using a computer-generated (SAS Proc PLAN) randomization list, and subjects were assigned to one of the two treatment groups. The number of subjects varied at each time point due to drop-outs. A total of 94 subjects completed the study. The primary analysis was performed according to the intention-to-treat principle.

Normality of the data was checked using histograms and Kolmogorov-Smirnov test. Variables were checked for outliers using Horn's method using "Reference Intervals" package in R (<https://CRAN.Project.org/package=referenceIntervals>). For all variables, analyses were performed with and without outliers and output remained similar, so full data were used. Descriptive statistics were presented as mean ± SD or median (1st quartile-3rd quartile) as appropriate based on the distributions. Baseline characteristics were compared among treatment groups using the Wilcoxon rank-sum test for not normally distributed variables and the two independent samples t test otherwise.

A repeated-measures mixed-effects logistic regression model with random subject-specific intercept and unstructured covariance matrix was used to predict hypercalciuria (binary) and hypercalcaemia using the main effect "time" and the 2-way interaction effect term between time and group. SAS Proc GLIMMIX was used to implement this model. Repeated-measures linear mixed-effects models with random subject-specific intercept and trend were developed for log-transformed PTH, CTX and GFR. We considered the main effect time in addition to the 2-way interaction

term between time and group in all models, and unstructured variance-covariance matrix was used throughout. The significance of each term (interaction and main effects) is assessed via a traditional F test obtained from the mixed-effects models. SAS Proc MIXED was used to employ these models. Missing data were handled by these mixed-effects models under the assumptions of ignorability.<sup>27,28</sup>

Secondary analyses were performed for vitamin D metabolites [25(OH)D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub>] and PTH using baseline and final values only. Change (Final – Baseline) was computed for each of these variables and compared between treatment groups using Wilcoxon rank-sum test. All calculations were performed using SAS software (SAS version 9.4; SAS Institute, Cary, NC, USA) and R (<https://www.Rproject.org>). Results were considered statistically significant when  $P < 0.05$ .

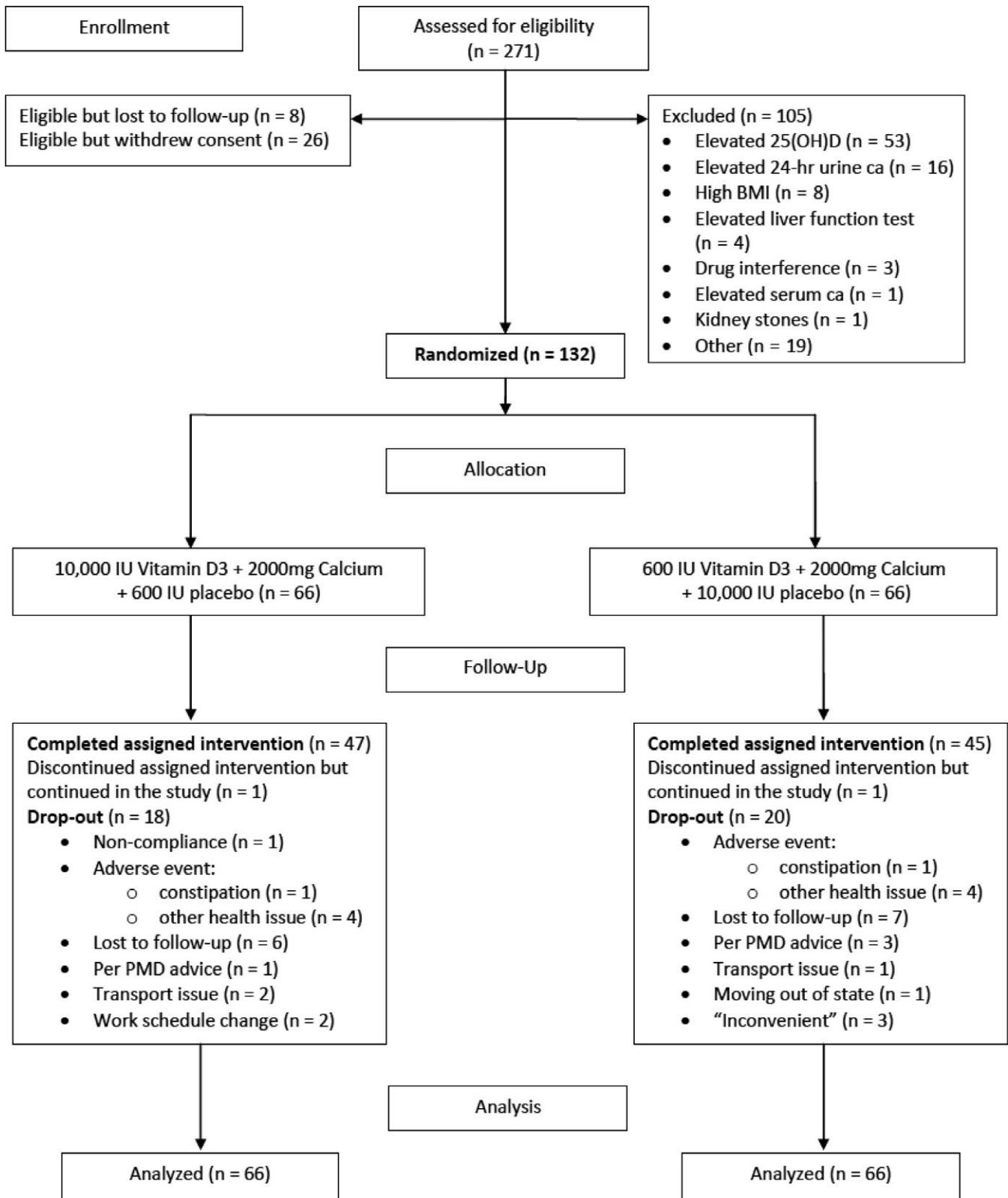
## 3 | RESULTS

### 3.1 | Study progress

A flow diagram for the study is given in Figure 1. A total of 271 subjects were screened for eligibility for the study. Of those, 105 were excluded based on eligibility criteria, and 34 were eligible but were lost to follow-up or withdrew their consent prior to randomization. The remaining 132 screened subjects were eligible and randomized into the study, with 66 subjects each in the high vitamin D dose group and the 600 IU vitamin D/day group. Forty-seven subjects in the high vitamin D dose group and 45 subjects in the 600 IU vitamin D/day group completed the assigned intervention. In the high vitamin D dose group, one subject discontinued supplements but continued in the study, and there were 18 drop-outs. Of the drop-outs, only one was due to constipation. In the 600 IU/day group, there was also one subject who discontinued supplements but continued in the study, and there were 20 drop-outs, with only one being due to constipation. All 66 subjects from each group were included in the analysis.

### 3.2 | Demographics, baseline and final values (Table 1)

Clinical characteristics and baseline values are given in Table 1. Average age was 61.5 years and BMI was 27.2. Mean serum 25(OH) D was above the RDA-associated level (20 ng/mL), and no participants were vitamin D deficient using IOM guidelines. Median (q1-q3) dietary calcium intake at baseline was 878 (628-1114) mg/day in the high D group and 900 (675-1214) mg/day in the 600 IU/day group. At 12 months, median (q1-q3) total intake was 1986 (1779-2136) mg/day and 1843 (1728-1986) mg/day for the high and low vitamin D dose groups, respectively. Serum 25(OH)D at baseline was similar in both groups. At 12 months, the values rose by  $33.7 \pm 6.1$  ng/mL and  $8.6 \pm 26.4$  ng/mL in the high and low dose vitamin D groups, respectively. 24-hour urine calcium did not differ between the two groups at baseline.



**FIGURE 1** Flow diagram for the study.

### 3.3 | Hypercalciuria

Hypercalciuria was defined as a 24-hour urine calcium excretion over 250 mg, the generally accepted value for white women.<sup>29,30</sup>

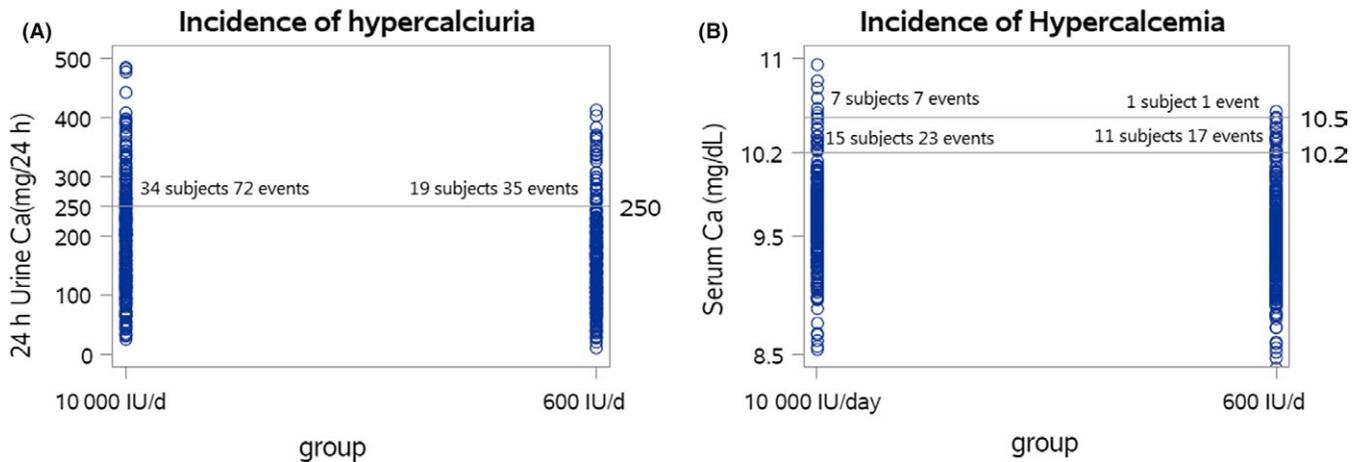
Of the 34 subjects with an instance of hypercalciuria in the high D group, 14 developed hypercalciuria once, 15 developed hypercalciuria 2-3 times, and 5 subjects developed hypercalciuria four times during the course of the study. Of the 19 subjects from the 600 IU/

**TABLE 1** Baseline and final values of demographics and clinical variables

	10 000 IU/day		600 IU/day		P-value for baseline comparison <sup>a</sup>
	Baseline (N = 66)	Final (N = 48)	Baseline (N = 66)	Final (N = 46)	
<b>Demographics</b>					
Age (years)	61.0 (57.5-67.9)	62.4 (56.9-70.7)	62.2 (58.2-68.2)	64.3 (59.6-70.9)	0.301
BMI (kg/m <sup>2</sup> )	28.0 (24.9-31.2)	27.2 (25.0-30.3)	27.0 (23.6-30.8)	27.6 (24.1-31.6)	0.484
Calcium intake (mg/day)	878 (628-1114)	1986 (1779-2136)	900 (675-1214)	1843 (1728-1986)	0.473
<b>Laboratories</b>					
25(OH)D <sub>3</sub> (ng/mL) <sup>b</sup>	27.5 ± 7.3	86.6 ± 26.4	27.9 ± 5.7	33.7 ± 6.1	0.798
1,25(OH) <sub>2</sub> D <sub>3</sub> (pg/mL)	46.3 (37.3-61.6)	50.0 (41.0-58.2)	42.6 (36.9-51.0)	43.9 (35.6-51.3)	0.042
PTH (pg/mL)	34.1 (25.5-45.6)	18.2 (11.2-23.5)	29.5 (24.4-40.9)	22.6 (16.0-29.3)	0.068
CTX (ng/mL)	0.6 (0.5-0.8)	0.5 (0.4-0.8)	0.5 (0.4-0.7)	0.4 (0.4-0.6)	0.2
Serum Ca (mg/dL)	9.5 (9.3-9.7)	9.7 (9.5-9.8)	9.6 (9.3-9.7)	9.5 (9.3-9.7)	0.784
Serum cr (mg/dL)	0.7 (0.6-0.7)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.951
Serum P (mg/dL) <sup>b</sup>	3.6 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	3.7 ± 0.5	0.609
24-hour urine Ca mg/day	120.7 (87.2-166.3)	229.1 (134.9-295.8)	117.4 (85.1-161.7)	167.9 (104.7-215.0)	0.971
Creatinine corrected 24-hour urine Ca	143.6 (97.0-184.3)	261.0 (163.1-300.0)	137.2 (94.8-171.8)	203.5 (133.3-232.3)	0.745

<sup>a</sup>P-values are from Wilcoxon rank-sum test for non-normally distributed variables and two independent samples t test for normally distributed variables.

<sup>b</sup>Normally distributed variable; non-normally distributed variables are presented as median (1st quartile-3rd quartile) and normally distributed presented as mean ± SD.

**FIGURE 2** A, Incidence of hypercalciuria. B, Incidence of Hypercalcemia

day group, 10 were hypercalciuric once, 7 were hypercalciuric 2-3 times and 2 were hypercalciuric four times during the study. See Figure 2A to visualize absolute values of 24-hr urinary calcium for subjects with and without hypercalciuria. The subjects with persistent hypercalciuria were not getting calcium supplements at the end of the study. Repeated-measures mixed-effects logistic regression model (generalized chi-square/DF = 0.63) for hypercalciuria revealed a significant time x group interaction term [slope=0.1068,  $F = 7.03$ , DF = (1, 319),  $P = 0.008$ ] indicating that the probability of hypercalciuria is higher among the high dose treatment (10 000 IU/day) group compared to the low dose group. The slope 0.1068 is the treatment effect per month. Therefore, the cumulative treatment

effect over the 12-month study duration is  $[0.1068 \times 12 = 1.28]$ . We exponentiated this estimate to compute the odds ratio for the entire study duration. The odds of developing hypercalciuria are 3.6 times higher [OR (95% CI) = 3.6(1.39, 9.3)] in the high dose group compared to the low dose group over time. This model was further adjusted for 1,25(OH)<sub>2</sub>D<sub>3</sub> as it differed significantly between treatment groups at baseline (Table 1). The time x group interaction term remained significant [OR(95% CI) = 3.3(1.3, 8.5), while 1,25(OH)<sub>2</sub>D<sub>3</sub> was not significant ( $P = 0.284$ ) in this adjusted model. The model for hypercalciuria was re-examined by adding calcium intake as a time-varying covariate. The adjusted OR (95% CI) for time x group interaction term was 3.3(1.3-8.6), which remained comparable.

The calcium intake was statistically significant (slope = 0.0013,  $P < 0.0001$ ) in the model.

### 3.4 | Hypercalcaemia

Hypercalcaemia was defined as a serum calcium  $>10.2$  mg/dL (laboratory upper range). 23% of patients had hypercalcaemia at least once during the study period in the high dose group (15/66) (15 patients had 23 hypercalcaemic events) compared to 17% (11/66) (11 patients had 17 hypercalcaemic events) in the low dose group (see Figure 2B). Repeated-measures mixed-effects logistic regression model (generalized chi-square/ $df = 0.46$ ) for hypercalcaemia revealed a non-significant time  $\times$  group interaction term [slope =  $-0.0148$ ,  $F = 0.08$ ,  $df = (1, 357)$ ,  $P = 0.772$ ] indicating that the occurrence of hypercalcaemia over time is not different in the high dose treatment (10 000 IU/day) group compared to the low dose group [OR (95% CI) for the study period =  $0.84(0.25, 2.79)$ ]. Using serum calcium cut-off  $>10.5$ , we found 7 subjects (episodes) in the high dose group and 1 in the low dose group. Among those with hypercalciuria, there were 6 hypercalcaemic (serum calcium  $>10.2$  mg/dL) subjects in the high dose group and 4 in the low dose group. Using serum calcium cut-off  $>10.5$  mg/dL, only 2 subjects were hypercalcaemic in the high dose group and none in the low dose group.

Hypercalcaemia was also computed after correcting serum calcium for albumin [(4.4-Serum Albumin g/dL) $\times 0.8$  + Serum calcium mg/dL]. For albumin-corrected serum calcium, 21% of patients had hypercalcaemia at least once during the study duration in the higher dose group (14/66) (14 patients had 20 hypercalcaemic events) compared to 17% (11/66) (11 patients had 17 hypercalcaemic events) in the low dose group; odds ratio (95% CI) for the study duration =  $0.74(0.22, 2.4)$ , not statistically significant.

### 3.5 | CTX and PTH

For CTX, the times  $\times$  group interaction terms were not significant. However, the main effect (time) was significant. The main effect time [slope =  $-0.001$  (0.006),  $F = 15.2$ ,  $df = 1, 385$ ,  $P < 0.001$ ] suggested an overall decrease in CTX from the baseline over time. The linear mixed-effects model for PTH (pg/mL) revealed a significant time  $\times$  group interaction effect (slope for high D group =  $-0.016$ ,  $F = 5.18$ ,  $df = 1, 520$ ,  $P = 0.023$ ) suggesting a significant decrease in PTH over time for the patients in the high D group compared to the 600 IU/day group.

### 3.6 | Relationship of vitamin D metabolites and PTH to hypercalciuria

Vitamin D metabolite data measured by liquid chromatography/mass spectrometry (LC/QMS) were only available at baseline and final time points (Table 1). Change (12 months – Baseline) variables were created for 25(OH)D<sub>3</sub>, and 1,25(OH)<sub>2</sub>D<sub>3</sub> as well as for PTH, then compared between groups using Wilcoxon rank-sum test. There

was a significantly higher increase in serum 25(OH)D<sub>3</sub> in the high D group compared to the 600 IU/day group ( $P < 0.0001$ ). Decrease in PTH was significantly greater in the high dose group compared to the low dose group. The change in 1,25(OH)<sub>2</sub>D<sub>3</sub> was not significant between groups ( $P = 0.380$ ).

### 3.7 | Adverse events

There were 37 unique patients who had 64 adverse events in the high D group compared to 38 unique patients who had 67 adverse events in the 600 IU/day group. There appears to be no difference in adverse events between groups.

### 3.8 | Adherence

Adherence was evaluated by pill count. In the high vitamin D group, there was 85% compliance for the vitamin D and 81% for calcium. Comparable adherence was found in the 600 IU/day group with 87% and 84%, respectively.

## 4 | DISCUSSION

We found that a high dose of vitamin D co-administered with calcium supplements is associated with frequent episodes of hypercalciuria. Hypercalciuria also occurred in response to calcium supplements and just 600 IU/day of vitamin D (800 IU/day total intake). The high intake of calcium, similar to the quantity of calcium supplements frequently recommended to patients, was probably the primary cause of hypercalciuria in the calcium plus 600 IU/day vitamin D group. Other studies have reported hypercalcaemia with calcium supplements or with vitamin D.<sup>20,31</sup> Pending further studies, the IOM UL for vitamin D (4000 IU/day) should be used rather than the high intake proposed in the Endocrine Society Guideline.

In the Women's Health Initiative [WHI], there was a 17% increase in kidney stones.<sup>32</sup> Total intake of calcium in the WHI was 2100 mg (1000 mg from supplements) and vitamin D was 765 IU. Thus, this intake was similar to our 600 IU/day vitamin D group (with an additional 200 IU/day from diet). The WHI was a long-term study; most studies of calcium and vitamin D supplements, including ours, were of too short duration or too small to detect kidney stones. Assuming that the kidney stones are related to episodes of hypercalciuria, an even higher incidence of kidney stones would be expected with high dose vitamin D intake in the presence of 1200 mg/day of calcium supplements. Moreover, there have been studies that have addressed concern about the safety of calcium supplements in terms of mortality, cardiovascular and cerebrovascular disease and high doses of vitamin D and excess mortality, falls and fracture.<sup>32-38</sup> Our study adds concern about the harms of co-administration of these supplements at high intakes.

We found a decline in PTH consistent with prior studies.<sup>22,31</sup> Calcium supplements suppress PTH secretion as does vitamin D

supplementation. In a previous study with 4000 IU/day of vitamin D<sub>3</sub>, a decline was not seen in CTX in the vitamin D groups. In the current study with high dose D, there was a decline in CTX in both groups. This finding is significant because there has been concern that higher doses of vitamin D will increase bone resorption which was not the case here.

The possible explanation for greater incidence of hypercalciuria in the high D group is of interest. In the 2 groups, serum calcitriol was unchanged, and CTX and PTH declined. The PTH declined to a greater extent in the high D group. We observed this in other studies as well. Bone resorption did not increase (CTX decreased), so it is likely that the reduction in PTH changes tubular calcium reabsorption resulting in greater hypercalciuria. The use of 10,000 IU of vitamin D daily with 2000 mg of calcium should be considered as pharmacologic quantity of their nutrients.

A strength of our study is that it is the first report to examine toxicity of calcium with vitamin D supplements in healthy people as its primary aim. It confirms other reports where hypercalcaemia and hypercalciuria were noted as adverse effects. High intakes of vitamin D are clearly associated with greater incidence of hypercalciuria than an intake at the RDA (600-800 IU/day in adults). A weakness is that these episodes of hypercalciuria have not been proven to be related to kidney stone formation.<sup>38</sup> Moreover, our sample size was small so that it may not reflect the general population and cannot be extended to men or other ethnic or age groups. Further adverse outcomes cannot definitively be attributed to calcium or vitamin D, but only to their combined effects.

At baseline, mean serum 25(OH)D was above the RDA set by the Institute of Medicine [IOM] (but not for the value suggested by the Endocrine Society). After treatment, the mean serum 25(OH)D was 86.6 ng/mL, above the UL set by the IOM which is 20 ng/mL. It should be noted also that the analyses of our vitamin D supplements revealed that they were about 20% higher in content than for the 10 000 IU requested. This resulted from the practice recommended by the United States Pharmacopeia of manufacturing vitamin D 20% above its stated value in order to maintain shelf life. Although previous high dose vitamin D studies did not report on supplement analyses, the response to 12 000 IU should be roughly comparable to 10 000 IU because of curvilinearity of the dose-response curve of vitamin D intake.

In conclusion, we have shown that the UL intake of vitamin D advocated in The Endocrine Society Guidelines when co-administered with a calcium intake at the UL is associated with increased odds of hypercalciuria. Until further large-scale studies are performed the UL for vitamin D proposed by the IOM is to be preferred to that proposed by the Endocrine Society. The UL for calcium intake should also be re-examined. The increased risk of kidney stones due to the addition of vitamin D to calcium supplements should be evaluated in large population studies.

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## CONFLICT OF INTEREST

All Authors read and approved the final manuscript. None of the authors had a conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

The Author's responsibilities were as follows—JFA designed the study, wrote the manuscript and supervised the study. SK, AS and GU were ECRIP research fellows that worked on the study in the Bone Mineral Research Center. MM supervised the study. AH was instrumental in doing the laboratory studies of vitamin D. Shahidul Islam participated in the design of the study and analysed the data. The Bone Mineral Research Center would also like to acknowledge the Winthrop Research Institute, the pharmacists, Jane Greensher (study coordinator) and Lynn Maier, typist.

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