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HIGH DOSE VITAMIN D2 SUPPLEMENTATION FOR A YEAR DOES NOT CAUSE SERIOUS ADVERSE EVENTS INCLUDING EMERGENCY ROOM VISITS AND HOSPITALIZATIONS IN AFRICAN AMERICAN MEN WITH HIGH BURDEN OF CHRONIC DISEASE

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The observational studies of vitamin D supplements had been associated with improved health outcomes without significant adverse consequences (1,2). The randomized controlled trials (RCT), however, had been inconclusive and vitamin D combined with calcium supplements increased the risk of nephrolithiasis (1,2). The Institute of Medicine warned about using high doses of vitamin D and suggested 25(OH)D serum level >50 ng/ml as possibly associated with higher health risks (2). There had been no detail reports of serious adverse events (SAE) from a long-term (a year) RCT using high dose (50,000 IU/week) vitamin D (1). The present study examined SAE from a high dose vitamin D supplement in African American men (AAM).

This sub-study was ancillary to “D vitamin Intervention in Veteran Administration (DIVA)” trial described elsewhere (3). Briefly, the double blind RCT tested the effect of 12-month high dose vitamin D on glycemic control in 35–85 year-old AAM with dysglycemia (A1C 5.7–6.4%) and hypovitaminosis D (25(OH)D 5.0–29 ng/ml). All subjects received cholecalciferol (D3) 400 IU/day and either weekly ergocalciferol (D2) 50,000 IU (Pliva Co) or placebo. The dose of D2 was adjusted in a blinded manner by the research pharmacist at 3, 6, and 9-month visits to keep 25(OH)D in 40–100 ng/ml range. The SAE including emergency room (ER) visits and hospitalizations were collected from Computerized Patient Record System (CPRS) at three time points: a year prior to the trial (T0), a year of the trial (T1) and a year after the trial (T2). To account for all possible vitamin D-related SAE we designated the main outcome as total SAE including combined number of ER visits and hospitalizations during and after the trial (T1+T2).

The mean dose of D2 was 62,762 (range 50,000 – 88,460 IU/week) (Table 1) and calcium (combined dietary and supplemental) intake was 1000 mg/day. Disease burden was high with average number of 4 medical conditions (range 0 – 8) and 6.5 medications (range 0 –

17) per person. A total of 373 SAE over a 3-year period were equally distributed among T0 (N=141), T1 (N=110) and T2 (N=122) (Table 1). On average, there were 19 hospitalizations and 42 emergency room visits per 100 subjects per year. There were no differences in SAE between placebo vs vitamin D groups including comparison of the number of subjects with SAE or the number of SAE events per group (Table 1). The most common SAE were musculoskeletal (26%), psychiatric (21%), respiratory (13%) and cardiovascular (10%) conditions. There were no incidental kidney stones. Correlation analysis for the main outcome (SAE of T1+T2) showed association with T0 hospitalizations ($r=0.43$, $p<0.001$) and T0 ER visits ($r=0.53$, $p<0.001$). Regression analysis showed that the only significant predictors for the main outcome were T0 hospitalizations (coefficient estimate 0.677, 95% CI 0.543 – 0.812, $p<0.0001$) and T0 ER visits (coefficient estimate 0.629, 95% CI 0.458 – 0.801, $p<0.0001$). Therefore, high dose vitamin D supplementation for a year did not cause an increase in kidney stones or serious adverse events in African American men with high burden of chronic disease.

References

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Table 1

Serious Adverse Events over 3-year period in the subjects from the double-blind randomized controlled trial (RCT) of a year-long high dose vitamin D supplements in African American male veterans with hypovitaminosis D and prediabetes *

Characteristics*	Placebo, n=102	Vitamin D, n=103	P value
Vitamin D supplements			
D3 daily dose, IU	400	400	
D2 weekly dose, IU	0	62,762 ± 10,772	
Age, years	59. ± 2 6.0	58.8 ± 5.9	0.70
BMI, kg/m ²	32.0 ± 2.8	32.8 ± 3.2	0.15
SBP, mmHg	137 ± 16	134 ± 12	0.34
Serum 25(OH)D, ng/ml			
Baseline, prior to RCT	14.0 ± 4.8	14.7 ± 4.7	0.39
Final, 12 months of RCT	17.7 ± 5.6	50.1 ± 16.7	<0.001
Serum calcium, mg/dl			
Baseline, prior to RCT	9.2 ± 0.3	9.1 ± 0.3	0.23
Final, 12 months of RCT	9.3 ± 0.3	9.4 ± 0.4	0.20
Serious Adverse Events			
Hospitalizations			
A year prior to RCT	12 [18]	16 [25]	0.36
A year of RCT	15 [25]	10 [17]	0.42
A year after RCT	11 [13]	14 [19]	0.51
Emergency Room visits			
A year prior to RCT	30 [60]	28 [38]	0.68
A year of RCT	21 [26]	29 [42]	0.82
A year after RCT	27 [43]	31 [47]	0.48
Total SAE			
A year prior to RCT	42 [78]	34 [63]	0.34
A year of RCT	36 [51]	39 [59]	0.34
A year after RCT	38 [56]	45 [66]	0.45

* Values are Mean ± SD, values for SAE are numbers of subjects [number of events]. P values are from independent t tests (continuous) or chi-square tests (categorical) between groups. Age, BMI and SBP are at the Final study visit. The SAE were collected from the chart review and included Hospitalizations and Emergency Room visits during the year prior to RCT, a year during RCT and a year after RCT. There were no reports of kidney stones at any time.

Abbreviations: BMI=Body mass index, D3=Cholecalciferol, D2=Ergocalciferol, SAE=serious adverse events, SBP=systolic blood pressure, Total SAE= Emergency Room visits plus hospitalizations.