The Effect of Vitamin D on Aldosterone and Health Status in Patients With Heart Failure

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ABSTRACT

Background: Vitamin D deficiency is associated with heart failure (HF) events, and in animal models vitamin D down-regulates renin-angiotensin-aldosterone system hormones.

Methods: Patients with New York Heart Association (NYHA) functional class II−IV HF and a 25OH-D level ≤37.5 ng/mL received 50,000 IU vitamin D_3 weekly (n = 31) or placebo (n = 33) for 6 months. Serum aldosterone, renin, echocardiography, and health status were determined at baseline and 6 months.

Results: Mean age of participants was 65.9 ± 10.4 years, 48% were women, 64% were African American, mean ejection fraction was 37.6 ± 13.9%, 36% were in NYHA functional class III, and 64% were in class II. The vitamin D group increased serum 25OH-D (19.1 ± 9.3 to 61.7 ± 20.3 ng/mL) and the placebo group did not (17.8 ± 9.0 to 17.4 ± 9.8 ng/mL). Aldosterone decreased in the vitamin D group (10.0 ± 11.9 to 6.2 ± 11.6 ng/dL) and not in the placebo group (8.9 ± 8.6 to 9.0 ± 12.4 ng/dL; $P = .02$). There was no difference between groups in renin, echocardiographic measures, or health status from baseline to 6 months. Modeling indicated that variables which predicted change in aldosterone included receiving vitamin D, increasing age, African American race, and lower glomerular filtration rate.

Conclusions: Vitamin D_3 repletion decreases aldosterone in patients with HF and low serum vitamin D. Vitamin D may be an important adjunct to standard HF therapy. Further study will assess if vitamin D provides long-term benefit for patients with HF. (*J Cardiac Fail 2014;20:334−342*)

Key Words: Hormones, heart failure, aldosterone, health status, vitamin D.

Vitamin D has the potential to improve the symptoms of heart failure (HF) and to modulate the disease. Vitamin D deficiency has been associated with worse cardiovascular outcomes for patients with and without HF.[1−3] Vitamin D supplementation can reduce blood pressure and improve skeletal muscle function and strength.[4,5] Animal studies suggest that active vitamin D down-regulates the renin-angiotensin-aldosterone system (RAAS), reduces retention of salt and water, and reduces myocardial hypertrophy.[6,7] However, there are few trials of vitamin D therapy in patients with HF, and trials to date show mixed benefit on physical performance outcomes and inflammation.[8−10]

Our recent pilot trial of vitamin D_3 for 6 months did not improve aerobic capacity or skeletal muscle strength in patients with HF who were ≥50 years old.[8] Here we present secondary data analysis from the randomized trial of high-dose vitamin D_3 in patients with HF and its effect on the RAAS. We hypothesized that patients with HF who were

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treated with vitamin D plus oral calcium for 6 months would decrease serum concentrations of hormones and biomarkers (renin, aldosterone, C-reactive protein [CRP], and N-terminal pro−B-type natriuretic peptide [NT-proBNP]), decrease ventricular mass, improve diastolic function, and improve health status compared with those who took placebo with calcium.

Methods

A description of the methods and the primary trial results have been published previously.[8] Briefly, this was a randomized controlled double-blind placebo-controlled trial of 50,000 IU vitamin D_3 versus placebo weekly for 6 months in patients with HF. Both groups received 800 mg calcium citrate daily. The trial was approved by the Institutional Review Board at University Hospitals, Case Medical Center. Eligible subjects provided informed consent and were randomly assigned 1:1 to receive 50,000 IU vitamin D_3 or matching placebo.

Randomization and Allocation

Patients were randomized in a permuted block scheme according to race, age, and sex. Group assignment remained concealed from study staff, participants, and investigators until data collection was complete.

Patients

Patients aged ≥50 years in New York Heart Association (NYHA) functional class II−IV regardless of ejection fraction were recruited from academic HF and general cardiology practices. Patients were required to be on maximal tolerated doses of evidenced-based HF medications according to the primary cardiologist. Serum 25-hydroxyvitamin D (25OH-D) concentration ≤37.5 ng/mL was required. Exclusion criteria included primary hyperparathyroidism, sarcoidosis, hypercalcemia, nephrolithiasis, osteoporosis, creatinine >2.5 mg/dL, daily intake of vitamin D >400 IU, corticosteroid, parathyroid hormone (PTH), androgen, or estrogen use, current illicit drug use or ≥3 alcoholic drinks daily, advanced cancer, or myocardial infarction in the preceding 6 months. Also excluded was use of medications known to lower serum 25OH-D or the bioavailability of oral vitamin D, including: ketoconazole, colestipol, cholestyramine, mineral oil, phenobarbitol, and phenytoin. Patients were screened first by medical history and second by serum 25OH-D concentrations.

Measures

All blood samples were obtained from patients in the upright position. Blood was stored at 2−8°C.

Serum Analysis

Serum 25OH-D was measured with the use of chemiilluminescence immunoassay (ARUP, Salt Lake City, Utah) with an intra-assay coefficient of variation (CV) of 3%−6% and an interassay variability of 6%−11%.

PTH was measured with the use of chemiluminometric technology (Siemens Dimension Vista Systems, Newark, Delaware) by University Hospitals clinical laboratory.

Aldosterone was measured in duplicate to assure accuracy; the 2 measures were averaged for the final result. If the 2 measures were >20% different the test was rerun. The Siemens solid-phase Coat-A-Count radio immunoassay kits (Siemens Healthcare Diagnostics, Malvern, Pennsylvania) were used and had an intra-assay CV of 3.5% and an interassay variability of 6.9%.

NT-proBNP was measured in duplicate with the use of a sandwich immunoassay with electrochemiluminesence detection (Meso Scale Discovery, Gaithersburg, Maryland) with an intra-assay CV of 5.4% and an interassay variability of 7.8%.

Galectin-3 was measured in duplicate using enzyme-linked immunosorbent assay kits (BG Medicine, Waltham, Massachusetts) with an intra-assay CV of 3.3% and an interassay variability of 3.7%.

Plasma renin activity (PRA) was measured with the use of Gammacoat radioimmunoassay (ARUP) with an intra-assay CV of 5.5%−9.2% and an interassay variability of 7.1%−12.8%.

High-sensitivity (hs) CRP was measured by immunonephelometry with the use of the Siemens Dimension Vista analyzer (Siemens Healthcare Diagnostics) with an interassay variability of 5.0%.

Glomerular filtration rate (GFR) was calculated with the use of the Chronic Kidney Disease (CKD)−Epidemiology Collaboration equation.[11]

Urine Analysis

Spot urine calcium and creatinine were measured in the University Hospital clinical laboratory to evaluate safety of high-dose vitamin D. An increase in urinary calcium can indicate impending risk of hypercalcemia.

Echocardiography

A subset of participants (n = 34) was evaluated at baseline and 6 months with transthoracic 2-dimensional and Doppler echocardiography. The subset included all those who enrolled after the 1st year of the trial. Transthoracic echocardiograms were performed with the use of commercially available ultrasound systems (Vivid 7; GE Healthcare, Wauwatosa, Wisconsin; or iE33; Philips Medical Systems, Andover, Massachusetts). Participants were studied by one of 3 senior sonographers during quiet respiration in the left lateral decubitus position. Standard M-mode and 2-dimensional echocardiography and pulsed-wave spectral and Doppler tissue imaging echocardiographic parameters were obtained from parasternal and apical windows. M-Mode imaging was used to derive left ventricular (LV) dimensions, wall thicknesses, mass, and shortening fraction. Two-dimensional echocardiography was used to calculate LV ejection fraction from the 4- and 2-chamber acoustic windows with the use of the Simpson rule. Spectral Doppler−derived LV diastolic inflow (E and A waves, deceleration time) was recorded in the apical 4-chamber view, and early diastolic tissue Doppler velocities (e′) were measured at the septal and lateral corners of the mitral annulus. The ratios of E/A and E/e′ as well as deceleration time were measures of diastolic LV function. Images were stored digitally and analyzed randomly offline (Heartlab; Agfa, Hackensack, New Jersey) by a single investigator blinded to all clinical data. Three representative beats were averaged. All measurements were performed in accordance with American Society of Echocardiography guidelines.[12,13]

Kansas City Cardiomyopathy Questionnaire (KCCQ)[14]

The KCCQ was measured at baseline and 6 months. It is a 23-item self-administered instrument that gives an overall summary score but is also divided into 4 subscales (domains), including symptoms (frequency, severity, and recent change over time), physical limitations, social functioning, and quality of life. The questionnaire takes

~8−10 minutes to complete. Patients were assisted with answering the questions to assure comprehension. Scores range from 0 to 100; higher scores reflect better health status.

Statistical Analyses

Baseline demographics were summarized by means and standard deviations for continuous variables and frequency and proportions for categoric variables within study groups. The treatment effect (vitamin D vs placebo) was evaluated for each end point with the use of an analysis of covariance (ANCOVA) model that adjusts for baseline end point. Two multivariable models were constructed with the 6-month change in aldosterone as the end point. The larger model includes the covariates deemed to be the most clinically relevant, and the smaller model includes a further-reduced subset of covariates. All statistical analyses were performed with the use of R (Vienna, Austria).

Results

Recruitment, Retention, and Adherence

Patients were recruited from May 2007 to April 2011. Three hundred forty patients were screened for study inclusion, and 276 did not meet entry criteria (Fig. 1). Sixty-four were randomized and their data included in the analysis. Based on monthly pill counts, adherence was 100% in the vitamin D group and 99.5% in the placebo group. The vitamin D group had 90.7% and placebo group 90.8% adherence to the calcium pills.

Patient Characteristics

Mean age for the participants in the intervention group was 65.8 ± 10.6, 51.6% were women, and 61.3% were African American. For the placebo group, mean age was 66.0 ± 10.4, 45.5% were women, and 66.7% were African American. The majority of patients were nonischemic, mean ejection fraction was 37.6 ± 13.9%, and NYHA functional class was III in 36% and II in 64% (Table 1).

Effects on Serum 25OH-D, PTH, and Calcium

At 6 months, serum 25OH-D increased by 42.3 ± 16.4 ng/mL in the vitamin D group and decreased by −0.2 ± 6.6 ng/mL in the placebo group ($P = .001$). PTH decreased by −23.1 ± 40.0 pg/mL in the vitamin D group and by −3.1 ± 38.1 pg/mL in the placebo group ($P = .01$) (Figs. 2 and 3). Calcium concentrations had no significant change in either group.

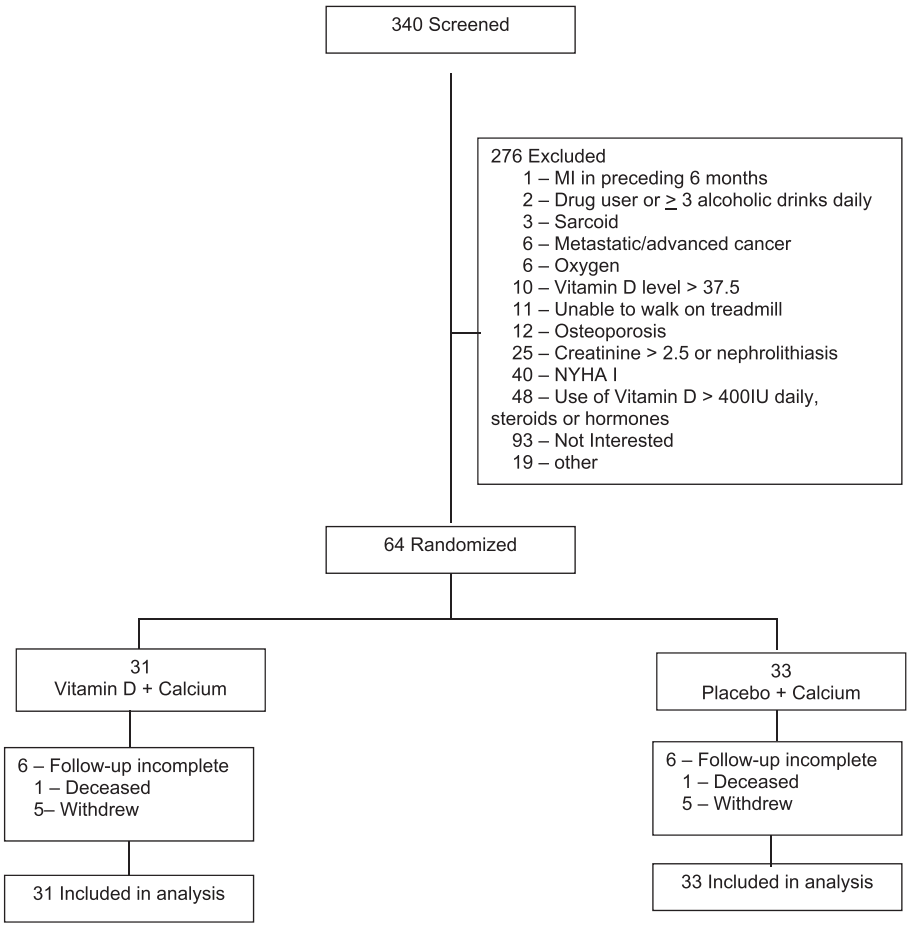

Fig. 1. Flow diagram. NYHA, New York Heart Association functional class.

Table 1. Baseline Demographics

Characteristic	n, if Different	Vitamin D (n = 31)	Placebo (n = 33)
Age (y), mean (SD)		65.8 ± 10.6	66.0 ± 10.4
Women, n (%)		16 (51.6)	15 (45.5)
African American, n (%)		19 (61.3)	22 (66.7)
BMI (kg/m^2), mean (SD)	30, 33	34.8 ± 7.2	31.3 ± 6.9
Ischemic etiology, n (%)		8 (25.8)	10 (30.3)
Ejection fraction (%), mean ± SD		39.2 ± 13.2	36.1 ± 14.5
NYHA functional class			
II, n (%)		17 (55)	24 (73)
III, n (%)		14 (45)	9 (27)
Hypertension, n (%)		26 (83.9)	28 (84.8)
Hyperlipidemia, n (%)		26 (83.9)	25 (75.8)
Diabetes, n (%)		16 (51.6)	14 (42.4)
Pulmonary disease,* n (%)		16 (51.6)	16 (48.5)
Depression, n (%)		10 (32.3)	10 (30.3)
Laboratory values			
25OH-D (ng/mL)		19.1 ± 9.3	17.8 ± 9.0
PTH (pg/mL)	30, 33	62.3 ± 44.3	72.8 ± 40.2
Plasma renin activity (ng mL^{-1} h^{-1})	29, 28	7.6 ± 13.4	6.7 ± 8.6
Aldosterone (ng/dL)	31, 31	10.0 ± 11.9	8.9 ± 8.6
CRP (mg/dL)	25, 26	5.8 ± 10.2	8.5 ± 27.2
NT-proBNP (pg/mL)	31, 31	2570 ± 3800	4880 ± 6390
Galectin-3 (ng/mL)	31, 31	17.9 ± 6.1	19.7 ± 6.4
Calcium		9.3 ± 0.5	9.2 ± 0.4
GFR	31, 32	65.5 ± 24.2	61.2 ± 19.9
Medications†			
ACE inhibitor, n (%)		20 (64.5)	22 (66.7)
Enalapril EQ dose (mg)		40, 32.8 (10, 80)	40, 30.2 (5, 80)
ARB, n (%)		8 (25.8)	9 (27.3)
Valsartan EQ dose (mg)		240, 215.0 (40, 320)	240, 202.2 (40, 320)
Beta-blocker, n (%)		29 (93.5)	28 (84.8)
Metoprolol EQ dose (mg)		150, 130.4 (25, 200)	175, 139.3 (25, 200)
Loop diuretic, n (%)		22 (71.0)	26 (78.8)
Furosemide EQ dose (mg)		40, 62.4 (6, 200)	40, 70.0 (10, 400)
Aldosterone antagonist, n (%)		7 (23)	13 (39)

BMI, body mass index; NYHA, New York Heart Association; PTH, parathyroid hormone; CRP, C-reactive protein; NT-proBNP, N-terminal pro−B-type natriuretic peptide; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; EQ, equivalent.
*Includes chronic obstructive pulmonary disease, emphysema, asthma, and sleep apnea.
†Doses are given in mean daily dose and converted to a standard medication.

Effect on Hormones and Biomarkers

Serum aldosterone changed from 10.0 ± 11.9 ng/dL to 6.3 ± 7.0 ng/dL (37% reduction) in the vitamin D group and from 8.9 ± 8.6 ng/dL to 9.0 ± 12.4 ng/dL in the placebo group. The ANCOVA model controlling for baseline aldosterone and group produced a treatment effect of −3.7 (P = .02). Change in PRA in the vitamin D group 7.6 ± 13.4 ng mL^{-1} h^{-1} to 6.3 ± 7.0 ng mL^{-1} h^{-1} and in the placebo group 6.7 ± 8.6 ng/mL to 9.2 ± 8 ng mL^{-1} h^{-1} (P = .2 for change between groups). There was no significant change between baseline and 6 month serum hsCRP, NT-proBNP, or galectin-3 (Fig. 3). Those patients with the lowest GFR tended to have the highest aldosterone at baseline (correlation −0.36; P = .004) and the largest decrease in aldosterone concentrations (Fig. 4). Univariate and multiple regression models with change in aldosterone as the dependent variable are shown in Table 2. The first model shows the relationship between demographics and the change in aldosterone. The second model adds clinical variables. There was no relationship between the change in aldosterone and medications (loop diuretics, angiotensin-converting enzyme (ACE)

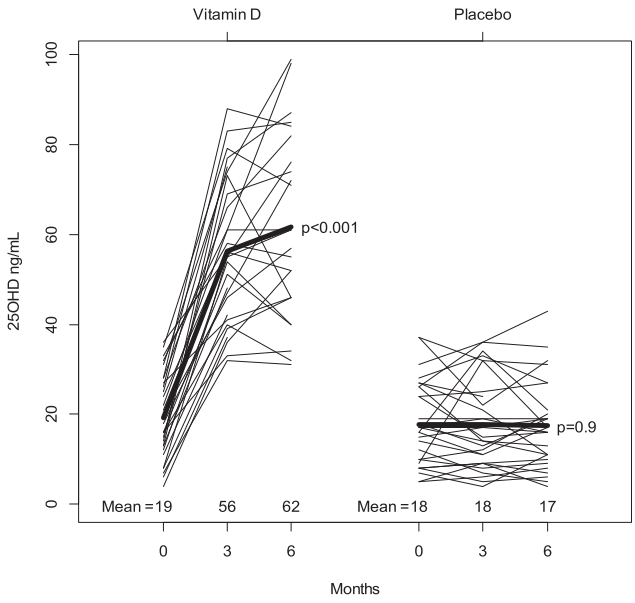

Fig. 2. Change in serum concentrations of 25OH-D in the vitamin D and placebo groups at baseline and 3 and 6 months.

inhibitor, angiotensin receptor blocker (ARB), aldosterone antagonist, or β-blocker).

Effect on Urinary Calcium/Creatinine Ratio

The spot urine calcium/creatinine ratio at baseline in the vitamin D group was 104.1 ± 60.0 mg/dL and in the placebo group was 87.4 ± 49.3 mg/dL (P = .3). The 3-month change in spot urine calcium/creatinine ratio in the vitamin D group was 27.9 ± 48.0 mg/dL and in the placebo group was 17 ± 58.2 mg/dL (P = .2).

Effect on Patient Symptoms, Echocardiography, and Health Status

There was no change in any echocardiographic variables within or between groups (Table 3). Health status, measured by the KCCQ, showed no statistical difference between groups, although there was a clinically relevant change (≥5 points) in all domains of the KCCQ[15] (Table 3). Outlier sensitivity analysis did not change results. There was no difference between groups in blood pressure or in those who reported worsening HF symptoms during the course of the study or in the number of patients who were hospitalized and/or received in-office intravenous diuretics.

Discussion

This secondary data analysis of a randomized controlled trial of vitamin D_3 in patients with HF indicates that repletion with vitamin D_3 may cause a decrease in serum aldosterone concentration in vitamin D−deficient patients with HF. Clinical effect was demonstrated only in an increase in the KCCQ scores (>5 points change) in the vitamin D group, albeit not a statistically significant increase. No other measures showed a clinical change, including echocardiographic changes in cardiac structure/remodeling, hsCRP, NT-proBNP, patient symptoms, or blood pressure. However, in other studies, the KCCQ has proven to be a sensitive measure of clinical change (better than NYHA functional class or the 6-minute walk test) for both patients

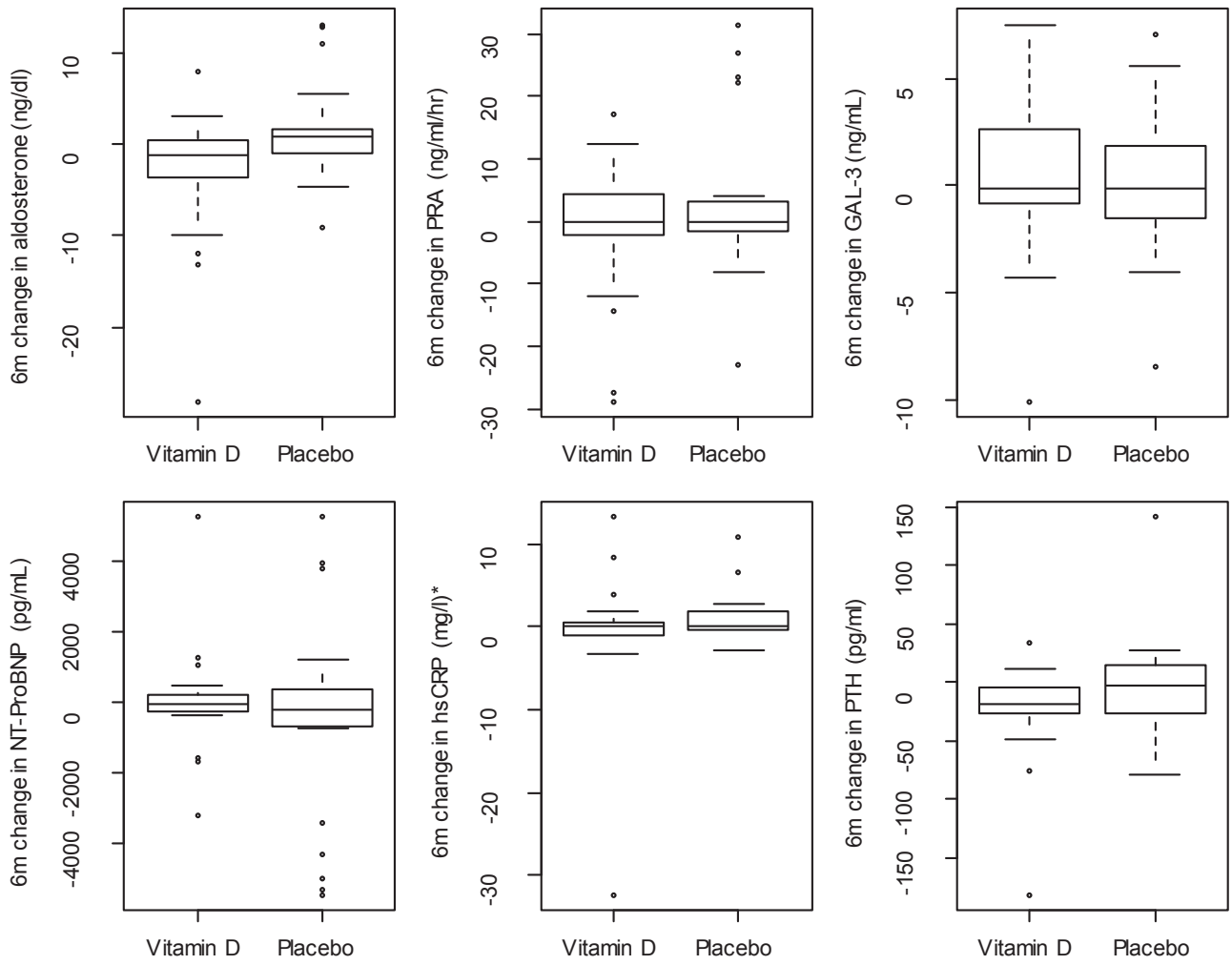

Fig. 3. Changes in biomarkers from baseline to 6 months in the vitamin D and placebo groups. *One CRP outlier suppressed in placebo group to compress the y-axis. PRA, plasma renin activity; GAL-3, galectin 3; hsCRP, high sensitivity C-reactive protein; PTH, parathyroid hormone.

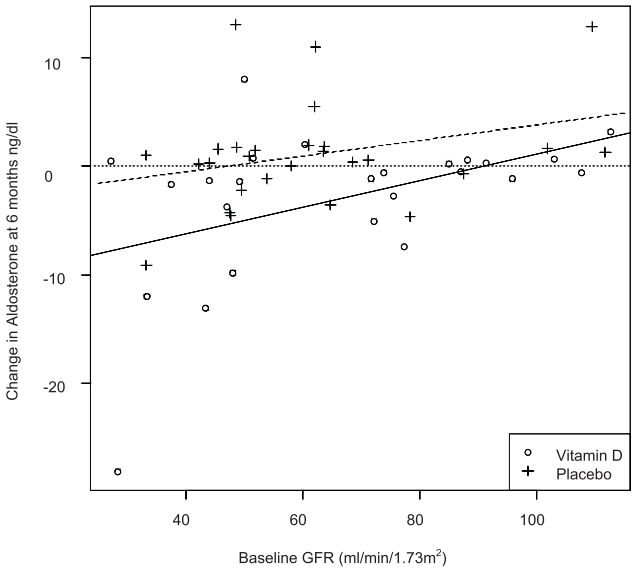

Fig. 4. Change in aldosterone according to baseline glomerular filtration rate (GFR).

who are worsening and those who are improving.[15,16] The vitamin D_3 dose of 50,000 IU did not cause hypercalcemia or hypercalciuria.

This is the first study in patients with HF to demonstrate a reduction in aldosterone with oral vitamin D_3. Two earlier studies investigated the effects of vitamin D in patients with HF. Witham et al studied 105 White patients and found no significant change in aldosterone; however, serum 25OH-D did not reach as high a concentration in the treatment group as in our study.[9] An open-label study by Schroten et al showed no change in aldosterone but a significant decrease in PRA[17] (discussed below). Another small study of patients with essential hypertension (not HF) showed a reduction in aldosterone concentrations of 30% with oral vitamin D_3.[18]

Aldosterone is important to the pathogenesis of HF, contributing to myocardial fibrosis, and blockade of aldosterone improves outcomes.[19,20] Much of the focus in HF therapeutics has been in RAAS blockade, but ACE inhibitors, diuretics, and aldosterone antagonists can all contribute to persistently elevated aldosterone concentrations, ie, aldosterone escape.[21,22] Higher serum aldosterone concentrations are associated with worse cardiovascular outcomes, especially in patients with lower GFR.[23] A retrospective study of vitamin D treatment reduced CV events in patients with CKD.[24] However, the clinical benefit of reducing aldosterone concentrations is unclear in the context modern HF therapy.

The amount of decrease in aldosterone in our trial was similar to that seen in the Valsartan Heart Failure Trial (Val-Heft), in which aldosterone declined by 34.6 pg/mL (3.46 ng/dL) and 31.9 pg/mL (3.19 ng/dL) at 4 and 12 months, respectively, in the treatment group.[25] However, despite a decline in aldosterone in Val-Heft, there was no relationship to improved outcomes.

In the complete linear regression model, age, treatment with vitamin D, being African American, and baseline GFR most strongly predict the change in aldosterone. In a study of hypertensive African American patients, vitamin D treatment led to a modest reduction in blood pressure.[4] The inverse relationship between GFR and aldosterone is consistent with limited animal and human data in CKD.[23,26] Those with CKD are known to have activated RAAS. Explanation as to why there was a more robust suppression of aldosterone for patients with lower GFR (as seen in Fig. 4) by vitamin D is theoretical. Patients with CKD (GFR <60 mL min^{-1} 1.73 m^{-2}) may have low incident $1,25(OH)_2D$ levels despite adequate 25OH-D levels.[27] In CKD, $1,25(OH)_2D$ production is dependent on the availability of 25OH-D in the circulation.[28] We therefore speculate that treatment with high-dose vitamin D increased $1,25(OH)_2D$ levels, resulting in more pronounced suppression of the RAAS as seen in animal models.

Although the PRA did not significantly decrease in the vitamin D group compared with the control group, a renin-mediated mechanism is reported in mouse models. Those studies support that vitamin D acts through down-regulation of RAAS. Vitamin D receptor knockout mice have hypertension and cardiac hypertrophy, and blood pressure normalizes by administration of captopril.[29] In wild-type mice, blockade of $1,25(OH)_2D$ increases renin expression, and with injection of $1,25(OH)_2D$ renin is suppressed.[7] Schroten et al reported a decrease in renin in human HF patients given vitamin D.[17] However, there are a number of design differences between our study and Schroten et al's that may explain the differences in our results. First, the study subjects from the Schroten et al trial were $>90\%$ male, all were White, and all had systolic failure. This is in contrast to our study, which was one-half female, more than one-half African American, and with mixed systolic and preserved systolic failure. In addition, the study period for the Schroten et al study was much shorter, only 6 weeks, with lower vitamin D dosing (2000 IU daily). However, our trial is limited by both its small size and the number of variables examined.

There are also studies in which high PTH levels are associated with HF.[30] In our study, the decrease in PTH was not independently associated with the change in aldosterone. However, it is impossible to examine the change in PTH separately from the change in 25OH-D, because they occurred simultaneously and are interrelated. There is growing evidence from both animals and humans that PTH may have an important role in cardiovascular disease and stimulate aldosterone secretions.[31]

Alternatively, there is a possibility that vitamin D could act through a renin-independent mechanism. In vitro study shows that the active form of vitamin D, $1,25(OH)_2D$, has a direct effect on adrenal cortical cells by down-regulating the enzymes in the steroidogenesis pathway. A nonsignificant decrease in aldosterone was seen with exposure to active vitamin D and significant decreases in other androgenic hormones.[32] This may be an alternative explanation

Table 2. Univariate and Multivariable Modeling for Change in Aldosterone at 6 Months

	Univariate	Multivariable Model 1	Multivariable Model 2
Covariate Effect	Effect Size (95% CI) *P* Value	Effect Size (95% CI) *P* Value	Effect Size (95% CI) *P* Value
Vitamin D group	−3.7 (−0.6, −6.8) .02	−4.4 (−7.3, −1.5) .003	−4.2 (−7.0, −1.3) .005
5 years of age	−0.7 (−1.5, 0.1) .07	−1.1 (−1.8, −0.3) .006	−1.0 (−1.7, −0.3) .008
Female	−1.4 (−4.7, 1.8) .38	−0.1 (−3.5, 3.3) .943	1.0 (−2.4, 4.3) .56
African American	−1.9 (−5.3, 1.5) .27	−2.6 (−6.6, 1.4) .194	−4.7 (−9.2, −0.2) .04
5 units of baseline 25OH-D	0.1 (0.0, 0.3) .09	0.8 (0.0, 1.7) .049	0.5 (−0.3, 1.4) .22
10 units of baseline PTH	0.0 (−0.4, 0.4) .85	—	0.2 (−0.2, 0.6) .25
Ischemic HF	−3.0 (−6.5, 0.5) .09	—	−2.1 (−5.6, 1.4) .23
NYHA III	−2.9 (−6.3, 0.5) .1	—	−2.2 (−5.3, 0.9) .16
10 units of baseline GFR	0.6 (−0.2, 1.3) .14	—	0.9 (0.1, 1.7) .04
Multivariable R^2	—	.43	.53

In each model, baseline aldosterone is included. Abbreviations as in Table 1.

if a lowering of aldosterone is not mediated through renin, and it requires more study.

Nutritional vitamin D is easily attainable and inexpensive. RAAS hormones are a major contributor to retention of sodium and water in HF pathophysiology, and drugs that block the RAAS control symptoms and prolong life. If vitamin D truly down-regulates aldosterone, it may be an important therapeutic addition to standard HF therapies, especially in patients with CKD. HF patients who do not tolerate RAAS blockade or who have aldosterone escape may also be a group of patients who would benefit. It is unknown if vitamin D treatment would result in improved symptom control, although the improvement in KCCQ scores in the treatment group indicates that this warrants further study.

Study Limitations

This is a secondary analysis from a small randomized controlled trial and results should be viewed in this context. Recruitment required that we screened >300 patients to enroll 64, but this is not atypical in vitamin D studies. The study is also limited by the testing of multiple end points, which should be taken into account when assessing the strength of evidence presented in this manuscript. The results from this trial do not provide any information regarding how vitamin D lowers aldosterone, and therefore the mechanism is theoretical. It is possible that PTH is the hormone that interacts and lowers serum aldosterone, but because PTH and 25OH-D change simultaneously it is impossible to tell which

Table 3. Change in Echocardiography and Health Status by Group

		6-Month Change in End Point		ANCOVA Model	
Echocardiogram	n*	Vitamin D	Placebo	Vitamin D−Placebo	*P* Value
Ejection fraction	19, 15	0.8 ± 4.5	2.3 ± 3.5	−0.8	.56
LV septal wall thickness	19, 15	0.0 ± 0.2	0.0 ± 0.1	0.0	.49
LV posterior wall thickness	19, 15	0.0 ± 0.2	0.0 ± 0.1	0.1	.25
LV mass	19, 15	−11 ± 40	−17 ± 47	−2	.89
LV mass index	19, 15	−5 ± 19	−8 ± 21	−1	.92
e/e′ septal mitral annulus	19, 14	−1.0 ± 5.2	−4.1 ± 8.0	1.1	.61
Quantitative EF, 4-chamber view	17, 14	−1.0 ± 13.8	10.4 ± 13.7	−3.7	.33
Quantitative EF, 2-chamber view	18, 14	1.1 ± 17.1	4.9 ± 11.4	0.9	.84
KCCQ					
Overall summary Score	25, 27	8.9 ± 20.4	2.2 ± 13.0	6.2	.16
Clinical summary score	25, 27	8.4 ± 17.0	0.3 ± 12.5	7.0	.09
Physical limitations	25, 27	7.1 ± 18.7	1.6 ± 14.1	5.1	.25
Total symptoms	25, 27	9.7 ± 22.8	-1.0 ± 16.7	7.5	.15
Quality of life	25, 27	9.0 ± 28.1	4.6 ± 17.5	6.4	.27
Social limitations	24, 27	9.9 ± 33.0	3.7 ± 19.9	5.6	.43

ANCOVA, analysis of covariance; EF, ejection fraction; LV, left ventricular; KCCQ, Kansas City Cardiomyopathy Questionnaire.
*A subset of participants was evaluated by echocardiography.

has the direct effect. Other unmeasured factors could have affected renin and aldosterone concentrations, such as dietary sodium content and serum potassium. Measurement of $1,25(OH)_2D$ levels were not performed and would have enhanced the understanding of our results. Only a subset of patients received echocardiographic measures, which should be studied in a larger sample.

Conclusion

A robust change in serum 25OH-D with a decrease in PTH resulted in a modest decrease in serum aldosterone in patients with HF without a statistically significant clinical benefit. Vitamin D_3 as an adjunct to standard HF therapy requires further study.

Disclosures

None.

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