Supplemental Vitamin D and Calcium in the Management of African Americans With Heart Failure Having Hypovitaminosis D

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Abstract: *Introduction:* A dyshomeostasis of macro- and micronutrients, including vitamin D and oxidative stress, are common pathophysiologic features in patients with congestive heart failure (CHF). In African Americans (AA) with CHF, reductions in plasma 25(OH)D are of moderate-to-marked severity (<20 ng/mL) and may be accompanied by ionized hypocalcemia with compensatory increases in serum parathyroid hormone (PTH). The management of hypovitaminosis D in AA with CHF has not been established. *Methods:* Herein, a 14-week regimen: an initial 8 weeks of oral ergocalciferol (50,000 IU once weekly); followed by a 6-week maintenance phase of cholecalciferol (1400 IU daily); and a $CaCO_3$ (1000 mg daily) supplement given throughout was designed and tested. Fourteen AA patients having a dilated (idiopathic) cardiomyopathy with reduced ejection fraction (EF, <35%) were enrolled: all completed the initial 8-week course; and 12 complied with the full 14 weeks. At baseline, 8 and/or 14 weeks, serum 25(OH)D and PTH; serum 8-isoprostane, a biomarker of lipid peroxidation, and echocardiographic EF were monitored. *Results:* Reduced 25(OH)D at entry (14.4 ± 1.3 ng/mL) was improved ($P < 0.05$) in all patients at 8 weeks (30.7 ± 3.2 ng/mL) and sustained ($P < 0.05$) at 14 weeks (30.9 ± 2.8 ng/mL). Serum PTH, abnormally increased in 5 patients at baseline (104.8 ± 8.2 pg/mL), was reduced at 8 and 14 weeks (74.4 ± 18.3 and 73.8 ± 13.0 pg/mL, respectively). Plasma 8-isoprostane at entry (136.1 ± 8.8 pg/mL) was reduced at 14 weeks (117.8 ± 7.8 pg/mL; $P < 0.05$), whereas baseline EF (24.3 ± 1.7%) was improved (31.3 ± 4.3%; $P < 0.05$). *Conclusions:* Thus, the 14-week course of supplemental vitamin D and $CaCO_3$ led to healthy 25(OH)D levels in AA with heart failure having vitamin D deficiency of moderate-to-marked severity. Albeit a small patient population, the findings suggest that this regimen may attenuate the accompanying secondary hyperparathyroidism and oxidative stress and improve ventricular function. **Key Indexing Terms:** Vitamin D; Calcium; Parathyroid hormone; Oxidative stress; Ejection fraction. **[Am J Med Sci 2011;341(2):113–118.]**

Hypovitaminosis D (plasma 25(OH)D <30 ng/mL) is associated with an increased risk of cardiovascular disease, including heart failure.[1] In individuals with pre-existing cardiovascular disease, reductions in plasma 25(OH)D are associated with ventricular dysfunction, death due to heart failure and sudden cardiac death.[2–5] Furthermore, African Americans (AA) are specifically at increased risk for cardiovascular disease, including heart failure.[6] In contrast to whites, heart failure in AA occurs at an earlier age, is more severe in its presentation often requiring hospitalization and is more progressive in nature with excessive morbidity and mortality.[7–11] These differences in incidence and severity of heart failure in AA have been attributed to various factors, including vitamin D deficiency.[12]

Hypovitaminosis D is prevalent in AA, including those having cardiovascular disease.[13] For AA living in the southern United States and having systolic heart failure with reduced ejection fraction (EF), vitamin D deficiency is not only prevalent but also of moderate-to-marked severity.[14] Reductions in plasma 25(OH)D could contribute further to compromised myocardial contractility with ventricular dilatation, adverse myocardial structural remodeling with fibrosis and mitral valvular calcification with functional incompetence.[15–20] Furthermore, AA having heart failure with vitamin D deficiency may also have abnormal increases in plasma parathyroid hormone (PTH; >65 pg/mL) in the absence of significant renal disease.[14] Secondary hyperparathyroidism has deleterious consequences on the heart, including PTH-mediated intracellular Ca^{2+} overloading of cardiac myocytes and mitochondria.[21–24] The excessive accumulation of mitochondrial Ca^{2+} leads to the induction of oxidative stress, opening of the mitochondrial permeability transition pore with ensuing organellar swelling and degeneration terminating in cellular necrosis.[25–27] Oxidative stress at a systemic level is an integral pathophysiologic feature of congestive heart failure (CHF).[28,29]

The overall optimal treatment of vitamin D deficiency in AA patients with heart failure remains uncertain.[30] Conventional diet alone cannot ensure adequate concentrations of vitamin D and therefore mandates the need for a vitamin D supplement.[30] The modest daily vitamin D supplements of 400 to 600 IU, recommended by the Institute of Medicine,[31] would seem to be grossly insufficient in AA given the severity of their vitamin D deficiency. Tangpricha and coworkers[32] addressed the efficacy of various repletion regimens and found a unit dose of 50,000 IU oral ergocalciferol, given weekly or monthly, was required to significantly raise serum 25(OH)D. We would further emphasize that an additional therapeutic target for such a supplement would be to reduce abnormal increases in serum PTH[33] and serologic biomarkers of oxidative stress (eg, plasma 8-isoprostane) while improving ventricular function.

Toward this end, we designed a regimen of supplemental vitamin D and calcium carbonate to examine whether it would attain these clinical end points in AA with heart failure having vitamin D deficiency. We selected 50,000 IU of ergocalciferol given weekly for 8 weeks followed by daily 1400 IU of oral

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cholecalciferol for 6 weeks, combined with supplemental $CaCO_3$ throughout the 14-week regimen.

METHODS

Study Population

Between the winter and spring of 2009–2010 we enrolled 14 AA outpatients (51.5 ± 2.3 years; 13 men) who were followed in the Cardiology Clinic at the Regional Medical Center, Memphis. Each had known systolic heart failure (EF <35%) of 6 months duration or more based on previous echocardiographic interrogation, together with vitamin D deficiency of moderate or marked severity, based on their plasma 25(OH)D levels of 10 to 20 ng/mL or <10 ng/mL, respectively. Serum creatinine was <2.0 mg/dL in all patients. Other exclusion criteria included a history of primary hyperparathyroidism, gastrointestinal malabsorption or metabolic bone disease.

At the time of study entry, all patients were clinically compensated without signs of CHF. For ≥2 weeks, they had been receiving stable doses of a medical regimen that included a loop diuretic, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, together with aldosterone receptor and beta adrenergic receptor antagonists. All patients remained on their medical regimen and were followed up as outpatients. They were examined at protocol weeks 8 and 14 to ascertain their clinical status and whether they remained compensated without signs of CHF.

Protocol

In addition to hypovitaminosis D, other baseline measurements included serum PTH, plasma 8-isoprostane and echocardiographic assessment of EF. A 14-week treatment protocol consisted of 2 phases: an initial phase aimed at improving plasma 25(OH)D levels to healthy levels, wherein 50,000 IU of oral ergocalciferol was given once weekly for 8 weeks, together with $CaCO_3$, 500 mg po twice daily; and a maintenance phase of 6 weeks during which time a daily oral vitamin D supplement of 1000 IU cholecalciferol was provided together with a multivitamin that included 400 IU vitamin D while $CaCO_3$ at 500 mg po twice daily was continued. Serial measurements of plasma 25(OH)D and PTH were obtained at weeks 8 and 14, whereas plasma 8-isoprostane and EF were monitored at week 14. The study was approved by the University of Tennessee Health Science Center institutional review board.

Serum 25(OH)D and PTH

Serum 25(OH)D and PTH were determined by the hospital laboratory service using the standard immunochemiluminometric assay technique.

Serum 8-Isoprostane

Plasma total 8-isoprostane (free and esterified) was measured using a commercially available EIA kit (Cayman Chemical Co., Ann Arbor, MI) following alkaline digestion and partial purification by C-18 solid-phase extraction according to kit instructions.

Serial Echocardiography

The baseline and 14-week transthoracic echocardiograms using 2-dimensional standard views were interpreted by one of us (MM) who was blinded as to whether the tracings had been recorded pre- or posttreatment.

Statistical Analysis

Group data are presented as mean ± SEM. Data were analyzed by one-way analysis of variance in SPSS software (version 18.0; SPSS, Chicago, IL). Multiple group comparisons were made by Scheffé F test. Significant differences between individual group means were assigned for P values <0.05.

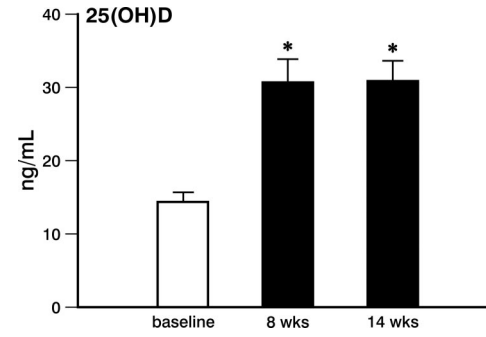

FIGURE 1. Serum 25(OH)D levels found at the beginning of study (baseline) and at 8 and 14 weeks of study protocol and treatment with vitamin D and $CaCO_3$ supplementation. *P < 0.05 versus baseline.

RESULTS

Plasma 25(OH)D Levels

In the 14 patients who completed the 8-week regimen, the plasma 25(OH)D level (14.4 ± 1.3 ng/mL) at the time of entry or baseline was markedly reduced ($P < 0.05$) and below the currently accepted normal level of 30 ng/mL in all patients (Figure 1). It was ≥20 ng/mL in all but 1 patient. The weekly 50,000 IU of oral ergocalciferol was effective in increasing 25(OH)D levels in all patients. At 8 weeks, plasma 25(OH)D levels had increased ($P < 0.05$) to 30.7 ± 3.2 ng/mL, with 80% of these patients achieving plasma 25(OH)D levels >25 ng/mL. The maintenance dose of vitamin D sustained the improvement in 25(OH)D at 14 weeks (30.9 ± 2.8 ng/mL).

Serum PTH Levels

In 9 of the 14 patients, baseline serum PTH levels (not shown) fell within the normal reference range (12–65 pg/mL) and maintained at 8 and14 weeks of treatment with vitamin D and $CaCO_3$. Serum PTH exceeded 65 pg/mL (104.8 ± 8.2 pg/mL; 79–127 pg/mL) at entry in 5 patients (Figure 2) and fell ($P < 0.05$) toward the normal reference range in response to 8 and 14 weeks of supplemental vitamin D with $CaCO_3$.

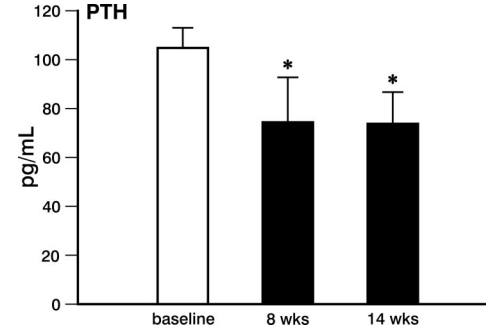

FIGURE 2. Serum parathyroid hormone (PTH) at baseline and at 8 and 14 weeks of the study in 5 patients who at the time of study enrollment had increased levels above the normal reference range (>65 pg/mL). *P < 0.05 versus baseline.

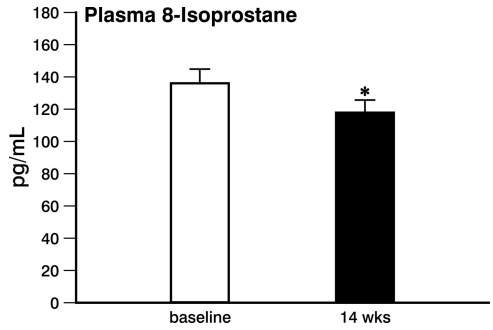

FIGURE 3. Plasma 8-isoprostane, a biomarker of oxidative stress and lipid peroxidation, at baseline and week 14 of the study. *$P < 0.05$ versus baseline.

Serum 8-Isoprostane Levels

As seen in Figure 3, baseline serum 8-isoprostane levels (136.1 ± 8.8 pg/mL) decreased ($P < 0.05$) to 117.8 ± 7.8 pg/mL at 14 weeks of treatment. Historical controls reported in the literature indicate serum 8-isoprostane levels in normal healthy adults to be 40 to 100 pg/mL.[34–36] We, therefore, cautiously suggest that our patients exhibited evidence of oxidative stress at the time of enrollment, which was attenuated during 14 weeks of treatment.

Ejection Fraction

Echocardiographically determined EF decreased below 35% in all study patients having a dilated (idiopathic) cardiomyopathy. EF obtained at the time of enrollment was 24.3 ± 1.7% and improved to 31.3 ± 4.3% at 14 weeks of treatment (Figure 4).

DISCUSSION

The optimal management of AA with heart failure having hypovitaminosis D remains unestablished. In this pilot study, we addressed the efficacy of a regimen of vitamin D supplement plus $CaCO_3$ and treatment protocol that we developed. Our objective was to significantly increase markedly depressed plasma 25(OH)D levels in AA having heart failure with vitamin D deficiency. The 2-part protocol called for an initial 8-week course of prescribed 50,000 IU weekly ergocalciferol plus 1000 mg daily $CaCO_3$ supplement followed by a 6-week course of across-the-counter 1400 IU vitamin D plus calcium daily. Major findings of this study were severalfold.

First, mean baseline plasma 25(OH)D level for the 14 patients at the time of study entry was 14.4 ± 1.3 ng/mL in keeping with significant hypovitaminosis D of moderate-to-marked severity in our patients. As we reported previously in 102 AA residing in Memphis, serum 25(OH)D levels were moderately to markedly reduced (<20 ng/mL) in more than 70% of those hospitalized because of their symptomatic heart failure. This was also the case in ambulatory AA outpatients with comparable EF and AA outpatients with heart disease but no heart failure.[14] Our regimen and protocol served to significantly increase baseline plasma 25(OH)D levels at 8 weeks and which was either sustained or caused to increase further at 14 weeks. These relatively consistent salutary findings, albeit obtained in a relatively small number of patients, encourage us to move forward using this regimen and therapeutic protocol in the management of AA residing in Memphis (35° N latitude) with heart failure and having vitamin D deficiency, are potentially contributory to irrespective of seasonal variation.

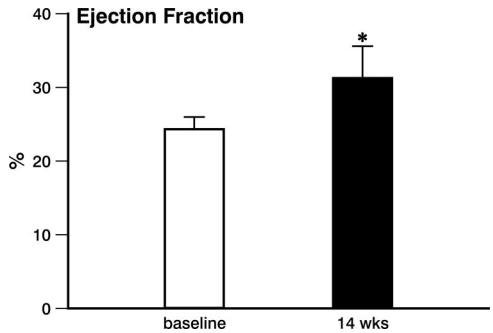

FIGURE 4. Ejection fraction obtained at the beginning of study and at 14 weeks of treatment. *$P < 0.05$ versus baseline.

Among the 14 AA patients recruited into this study with heart failure and hypovitaminosis D, 5 had secondary hyperparathyroidism with an abnormal increase in serum PTH (>65 pg/mL) at the time of study entry. This is consistent with our previous findings of ionized hypocalcemia and hypomagnesemia with increased serum PTH in some but not all AA patients with heart failure.[14,37] AA have a higher risk of developing secondary hyperparathyroidism.[38] This increased risk seems to be related to a marginal Ca^{2+} balance that is compromised by several factors. These include: lactose intolerance with an avoidance of dairy product consumption and thereby reduced dietary Ca^{2+} intake; increased dietary Na^{+}, which is hypercalciuric; hypoalbuminemia, albeit reversible, which accompanies a protein-losing enteropathy that appears during episodes of splanchnic congestion[39]; protracted activation of the renin-angiotensin-aldosterone system, where secondary aldosteronism enhances urinary and fecal excretion of Ca^{2+} and Mg^{2+}, leading to ionized hypocalcemia and hypomagnesemia with contemporaneous increases in serum PTH[23,40]; and treatment with a loop diuretic, which likewise accentuates urinary Ca^{2+} and Mg^{2+} excretion. Further evidence of secondary hyperparathyroidism in patients with heart failure is PTH-mediated bone resorption, which severely compromises bone mineral density and bone mineral content leading to osteopenia and osteoporosis that predisposes these patients to atraumatic fractures.[41–43]

Our second major finding was the decrease in elevated serum PTH seen in response to the vitamin D/$CaCO_3$ regimen. The increase in baseline serum PTH (105 pg/mL; 79–127 pg/mL) was reduced at 8 weeks treatment to levels which fell below or to the upper limit of the normal reference range (65 pg/mL); serum PTH remained at these reduced levels or decreased further at week 14. Increases in serum PTH, such as occur with primary or secondary hyperparathyroidism, have deleterious consequences in diverse tissues, including the heart. These include ventricular systolic dysfunction and skeletal myopathy, each of which resolve in response to parathyroidectomy or calcium channel blocker.[21,44–48] These findings implicate PTH-mediated intracellular Ca^{2+} overloading and induction of oxidative stress, together with vitamin D deficiency, as perhaps contributory to the dilated cardiomyopathy present in our patients.[21,23,46,49,50]

Our third major finding was the decrease in plasma 8-isoprostane from 136 ± 9 to 118 ± 8 pg/mL that accompanied the 14-week vitamin D/calcium regimen and protocol. This suggests that our regimen caused a reduction in oxidative stress and lipid peroxidation. Unfortunately, we did not establish our own control plasma 8-isoprostane levels obtained from

normal AA volunteers. However, the literature-based data suggest serum 8-isoprostane levels in healthy adults to be 40 to 100 pg/mL.[34–36] In keeping with reports from other laboratories, patients with heart failure have systemic evidence of oxidative stress with an increased production of oxygen-free radicals and lipid peroxidation.[51–54] We found that increased plasma 8-isoprostane could be reduced by our vitamin D/$CaCO_3$ supplement together with the associated increase in plasma 25(OH)D and decrease in serum PTH. In correcting vitamin D deficiency, the kidney's potential to elaborate renin and stimulate neurohormonal activation would be reduced.[55,56] Effector hormones of the renin-angiotensin-aldosterone and adrenergic nervous systems have each been mechanistically responsible for induction of oxidative stress in patients with CHF.[23,57,58] This includes intracellular Ca^{2+} overloading and the appearance of reactive oxygen species generation in diverse tissues that occur in response to calcitropic hormones, which include angiotensin II, aldosterone, PTH and the catecholamines, epinephrine and norepinephrine.[59–68]

The prevalence of hypovitaminosis D, often of marked severity, and its association with ventricular dilatation and reduced EF is high among patients with chronic cardiac failure, especially in AA.[14,19] Our final major finding is the favorable response in left ventricular EF that was found in a group of patients in whom we serially monitored echocardiograms. An improvement in EF was seen at 14 weeks of the protocol when plasma 25(OH)D levels had improved and increases in serum PTH had been attenuated. In children with dilated cardiomyopathy concomitant to vitamin D deficiency, the correction of this nutrient imbalance is associated with an improvement in ventricular function and reduction in ventricular chamber size.[69,70] This response has also been found in rodents, where vitamin D deficiency occurs secondary to the abolition of its receptor and where ventricular dilatation declines in response to vitamin D treatment.[17] As we found herein, a vitamin D/$CaCO_3$ supplement can also reduce increased plasma levels of PTH and thereby abrogate secondary hyperparathyroidism. PTH-treated rodents have reduced myocardial contractility with ventricular chamber dilatation.[24] A calcimimetic, which alters the Ca^{2+}-sensing threshold of the parathyroid glands in secondary hyperparathyroidism to reduce plasma PTH, improved ventricular structure and function.[71] In patients having primary hyperparathyroidism with ventricular systolic dysfunction, fractional shortening increases after parathyroidectomy.[72]

Our study has several limitations. First, the population of AA with heart failure and vitamin D deficiency we recruited and were able to follow for 14 weeks was rather small. This notwithstanding, the observations made in this group of patients allowed us to identify a vitamin D regimen and $CaCO_3$ supplement that we believe can now be applied to the overall management of hypovitaminosis D in AA with heart failure. It could also serve as a potential dosing regimen for a larger clinical study. Second, we could have followed up these patients for 6 months to further determine the response in ventricular and atrial chamber size and function. We could have prolonged the initial phase of treatment with ergocalciferol to 12 weeks to potentially achieve an even higher plasma 25(OH)D level before beginning the maintenance phase and use of an over-the-counter preparation. We will consider these measures in the future. Finally, we did not have a cohort-matched, untreated control group.

In summary, this pilot study, which consisted of an 8-week regimen of ergocalciferol (50,000 IU) given weekly, together with a 1000-mg $CaCO_3$ supplement in divided doses, raised the markedly reduced plasma 25(OH)D to healthy levels, which was then sustained by 1400 IU of daily cholecalciferol and $CaCO_3$ supplement in AA with reduced EF having vitamin D deficiency. In association with the improvement in plasma 25(OH)D was a reduction in abnormally increased plasma PTH and 8-isoprostane levels, coupled with an improvement in EF. This study has identified a treatment strategy that was not heretofore reported in AA patients with heart failure having hypovitaminosis D.

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