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Disclosures

Dr Boxer and this work are supported by the American Heart Association Scientist Development Grant 0635055N and by the KL2RR024990, Grant No. UL1 RR024989 from the National Center for Research Resources, a component of the National Institutes of Health.

From American Heart Journal

Serum 25-hydroxyvitamin D Concentration is Associated with Functional Capacity in Older Adults with Heart Failure

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Posted: 12/29/2010; American Heart Journal. 2010;160(5):893-899.

Abstract and Introduction

Abstract

Background Vitamin D is a fat-soluble hormone necessary for calcium homeostasis. Recently, studies have demonstrated that vitamin D may be important to the health of the cardiovascular system.

Methods Adults ≥50 years of age with heart failure were recruited for assessment of serum 25-hydroxyvitamin D (25OHD) concentrations. Cardiopulmonary exercise testing was used to assess functional capacity. Proximal muscle strength was evaluated with a Biodex leg press (Biodex, Shirley, NY), and health status was assessed with the Kansas City Cardiomyopathy Questionnaire. Univariate associations between physical performance and health status measures and 25OHD followed by a linear regression model were used to study associations, adjusting for other potential explanatory variables.

Results Forty adults 67.8 ± 10.9 years of age (55% women and 57.5% African American) with mean ejection fraction 40% were analyzed (New York Heart Association class II in 70% and class III in 30%). Comorbidities included 77.5% hypertension and 47.5% diabetes. The mean 25OHD concentration was 18.5 ± 9.1 ng/mL, and mean peak VO 2, 14 ± 4 mL/kg/min. In univariate regression analysis, 25OHD was positively associated with peak VO 2 (P = .045). Multivariable regression analysis sustained positive

association between 25OHD and peak VO_2 (P = .044) after adjusting for age, race, and respiratory exchange ratio (adjusted R^2 = 0.32). Association between proximal muscle strength with the 25OHD concentration was not significant. The Kansas City Cardiomyopathy Questionnaire physical limitation domain score was negatively associated with 25OHD (P = .04) but was not sustained in multivariable analysis.

Conclusions 25-Hydroxyvitamin D may be an important marker or modulator of functional capacity in patients with heart failure. Randomized controlled trials are needed to assess the effect of vitamin D repletion on functional performance.

Introduction

Heart failure (HF) can be a debilitating syndrome and is well known to cause functional limitations. Decreased cardiopulmonary reserve, abnormalities in muscle structure and function, and neuroendocrine derangements all contribute to a decline in physical performance. Symptoms of fatigue and dyspnea with exercise do not consistently correlate with resting hemodynamic parameters.[1] Coats[2] proposed the muscle hypothesis that integrates the skeletal muscle myopathy resulting from hormonal dysregulation and sympathetic excitation into the HF syndrome. This hypothesis has been important to understanding the physiologic changes, loss of muscle strength, and functional limitations in patients with HF. Furthermore, muscle strength has been found to be predictive of adverse outcomes.[3] Despite this, how to improve physical performance in patients with HF beyond standard therapies such as medications and/or aerobic training continues to be unclear.

Vitamin D deficiency has recently been found to be prevalent in those with cardiovascular diseases such as coronary disease and HF[4] as well as associated with cardiovascular risk and events.[5–7] There is evidence that vitamin D is associated with and may down-regulate inflammatory mediators[8,9] and promote cell growth and differentiation.[10] Vitamin D may be of particular importance in patients with HF because there is evidence that it down-regulates the renin-angiotensin system (RAAS)[11–13] and reduces blood pressure.[14]

In terms of function, studies have reported on the relationship of vitamin D concentrations and physical performance, with worse performance in those with lower 25OHD concentrations.[15–17] The most rapidly growing group of patients with HF are older adults, and because older adults are prone to vitamin D deficiency–related syndromes such as osteomalacia and osteoporosis, they may also be the most at risk for cardiovascular-related effects of vitamin D deficiency. Recently, we demonstrated that, in patients with HF, low concentration of 25OHD is associated with frailty and a shorter 6-minute walk distance.[16] Impaired walking has also been reported in association with low-serum 25OHD concentrations in non-HF populations.[17] Identification of the role 25OHD in functional decline and HF progression remains elusive. Whether vitamin D serves simply as a marker of poor health and nutrition versus a mediator of both muscle and cardiovascular function remains unclear.

To further evaluate the relationship of 25OHD concentrations with physical performance in HF, we assessed the cross-sectional relationship between 25OHD, functional capacity, and muscle strength in older adults with HF.

Methods

The study was approved by the institutional review board at University Hospitals/Case Medical Center. Participants were recruited from the HF and general cardiology practices at both the tertiary care site and satellite clinics. The study is a double-blinded, randomized, controlled trial of cholecalciferol versus placebo. Baseline data is presented in this article. Inclusion criteria included age ≥50 with either systolic or preserved systolic function HF, New York Heart Association (NYHA) classes II to IV at the time of study enrollment, maximum tolerated doses of HF medications as per the primary cardiologist before enrollment into the study, and 25OHD concentration <37.5 ng/mL. Potential participants were excluded for primary hyperparathyroidism or hypercalcemia; nephrolithiasis; a

diagnosis of osteoporosis; hemodialysis or peritoneal dialysis and/or creatinine of >2.5 mg/dL; current use of daily vitamin D >400 IU, corticosteroids, parathyroid hormone (PTH), androgen, or estrogen; current illicit drug user or ≥3 alcoholic drinks a day; metastatic or advanced cancer; and myocardial infarction in the preceding 6 months. Individuals who were on medications that could lower 25OHD concentrations or bioavailability of oral vitamin D administration including ketoconazole, colestipol, cholestyramine, mineral oil, phenobarbital, and phenytoin were also excluded. Screening for inclusion into the study was conducted as a 2-step process. Initially, volunteers were screened by medical history for the exclusion criteria listed above, and if qualified, a serum 25OHD concentration was collected.

Measures

Cardiopulmonary Stress Testing. Cardiopulmonary stress testing for functional capacity was performed using a modified Naughton protocol (Medical Graphics, St Paul, MN). Breath-by-breath online gas measurements were obtained at resting baseline and throughout the exercise protocol to measure minute ventilation ($\dot{V}E$), tidal volume (V_T), respiratory rate, oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$).[18] Peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ in the last minute of symptom-limited exercise. Ventilatory threshold defined as the $\dot{V}O_2$ at which anaerobic metabolism prevails in the periphery was measured by the V-slope method.[19] The Borg scale was used to assess patient effort, and patients were encouraged to rating of perceived exertion >15 (medium-hard)[20] and a respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$) >1.05. Respiratory exchange ratio serves as a measure of effort. Online electrocardiographic monitoring was obtained in addition to standard 12-lead electrocardiograms at rest and at the end of each stage of exercise. Gas exchange collection continued into recovery with 1 minute of active cool down at 1.5 mph; 0% elevation followed by resting while sitting in a chair until a return to baseline $\dot{V}O_2$ is observed or up to 6 minutes.

Isokinetic Muscle Testing. Muscular strength and power were assessed in the dominant leg using the Biodex System 3 Pro Isokinetic Dynamometer (Biodex, Shirley, NY). The protocol was designed specifically for the older adults, and before testing, each subject was given proper instruction on how to breathe correctly during testing to avoid Valsalva breath holding during the exercise. Quadriceps strength during knee extension and hamstring strength during knee flexion were measured with the subject in a seated position over a range of motion of approximately 90 ° using a speed of 60 ° s^{-1}. Muscle strength was assessed as peak torque in Newton meters (Nm) and also peak torque/body weight represented as Nm/kg.

Serum Analysis. Blood was collected and stored at 2 °C to 8 °C. 25OHD was measured by Chemiluminescent Immunoassay (ARUP, Salt Lake City, UT) with an intra-assay coefficient of variation of 3% and 6% and a between-assay variability of 6% to 11%. Parathyroid hormone was measured by Chemiluminometric Technology (Siemens Dimension Vista Systems, Newark, DE, by University Hospitals clinical laboratory). Creatinine, blood urea nitrogen, albumin, and calcium were measured at University Hospitals clinical laboratory.

Kansas City Cardiomyopathy Questionnaire. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered instrument that gives an overall clinical and 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 sensitivity of the KCCQ has been shown to be greater than that of the Minnesota Living with HF and the Short Form 36 questionnaires.[21] The questionnaire takes approximately 6 to 8 minutes to complete. Scores range from 0 to 100; higher scores reflect better health status.

Statistical Analyses

Pearson product moment correlation was used to assess the associations between the physical performance measures and 25OHD. A level of ≤.05 was considered significant. After the significant associations revealed by Pearson product moment correlation, we

used a linear regression model to study these associations after adjusting for other potential explanatory variables. To study the association between 25OHD and peak VO 2 (39 subjects successfully completed cardiopulmonary stress testing), we modeled the log (natural) transformed peak VO 2 to better meet normality assumptions of the linear regression model. Predictors that reached the .1 level of significance in univariate analysis were included in multivariable regression analysis. All potential pair-wise interactions were tested and were not significant. All analyses were conducted using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

Study Support. The study was supported by an American Heart Association Scientist Development Grant and the KL2 at Case Western Reserve University. The authors are solely responsible for the design and conduct of the study, all study analyses, and drafting and editing of the manuscript.

Results

Two-hundred seventeen patients with symptomatic HF, including systolic dysfunction and preserved systolic function, were screened for enrollment. Most patients' screen failed (29%) because of taking disqualifying medications including >400 IU of vitamin D a day. In addition, 12% had a creatinine >2.5 mg/dL, 12% had a history of kidney stones or osteoporosis, 8% were NYHA class I, and 10% were unable to walk on a treadmill or ride a bicycle because of mobility problems. Forty patients (mean age 67.8 ± 10.9 years, 55% women and 57.5% African American [AA], 67.5% nonischemic) were enrolled in the study as shown in Table I. The mean ejection fraction (EF) was 40% ± 14%, NYHA class II were 70%, and NYHA class III were 30%. Comorbidities included 77.5% with hypertension and 47.5% with diabetes. Mean serum 25OHD concentration was 18.5 ± 9.1 ng/mL. 25OHD varied by race, with AA having significantly lower 25OHD concentration than Caucasians (16 vs 22 ng/mL, $P = .04$). 25OHD concentration did not vary by age (<65 vs ≥65 years), body mass index (BMI; <30 vs ≥30 kg/m^2), or sex.

Table I. Characteristics of the study participants (n = 40)

Age (y), mean (SD)	67.8 ± 10.9
Sex, n (%)	
Men	18 (45)
Women	22 (55)
Race, n (%)	
AA	23 (57.5)
Caucasion	17 (42.5)
BMI (kg/m^2), mean (SD)	33.5 ± 7.6
Cause of HF, n (%)	
Ischemic	13 (32.5)
Nonischemic	27 (67.5)
NYHA class, n (%)	
II	28 (70)
III	12 (30)

Years with HF, mean (SD)	7.1 ± 6.4
EF, n (%)	39.5 ± 13.8
Diabetes, n (%)	19 (47.5)
Pulmonary disease, n (%)	19 (47.5)
Hyperlipidemia, n (%)	35 (87.5)
Peripheral vascular disease, n (%)	2 (5)
Hypertension, n (%)	31 (77.5)
Stroke, n (%)	5 (12.5)
Current smokers, n (%)	6 (15)
Serum Tests	
Calcium (mg/dL)	9.2 ± .4
Albumin (g/dL)	4.0 ± .3
Phosphorus (mg/dL)	3.5 ± .5
PTH (pg/mL)	61.8 ± 40.6
Serum blood urea nitrogen (mg/dL)	24 ± 11.2
Serum creatinine (mg/dL)	1.2 ± .4
Serum 25OHD (ng/mL)	18.5 ± 9.1
Medications*	
ACE inhibitor, n (%)	25 (62.5)
Enalapril EQ dose (mg)	30.8
Angiotensin inhibitor blocker, n (%)	11 (27.5)
Valsartan EQ dose (mg)	210.2
β-Blocker, n (%)	34 (85)
Metoprolol EQ dose (mg)	133.8
Loop diuretic, n (%)	30 (75)
Furosemide EQ dose (mg)	54.72
Aldosterone antagonist, n (%)	10 (25)
Spironolactone dose (mg)	19.8

*Doses are given in mean daily dose and converted to a standard medication.

The mean peak VO_2 was 14 ± 4 mL/kg per minute with a mean RER of 0.96 (range 0.76–1.12). The mean V_E/VCO_2 was 34.4 ±

7.6, indicating a mildly impaired ventilatory efficiency within the group. Peak torque adjusted for body weight in healthy populations usually reflects better strength in men than in women. In this cohort of patients, there was no statistical difference in peak torque between men and women. The KCCQ scores showed the lowest score at 65.4 ± 26 for the physical limitation domain and the highest of 75.8 ± 21.2 for the total symptom score (Table II).

Table II. Functional and health status testing

Cardiopulmonary stress test,* mean (SD)		
Peak Vo_2 (mL/kg/min)		14 ± 4
Men		14.8 ± 4.7
Women		13.4 ± 3.4
Percentage predicted Vo_2		68.6 ± 18.9
Peak exercise V_E/VCO_2		34.4 ± 7.6
Respiratory exchange ratio		.96 ± 0.1
Ventilatory threshold† (mL/kg/min)		13.8 ± 3.9
Exercise time (min)		8.5 ± 8.2
Isokinetic muscle testing at 60° s^{-1}		
Peak torque‡ (nm/kg)	**Extension**	**Flexion**
Men (n = 18)	38.3 ± 14.6	17.1 ± 6.7
Women (n = 21)	35.1 ± 12.5	16.1 ± 6.1
KCCQ		
Overall summary score	68.9 ± 22.9	
Subscales		
Physical limitation score	65.4 ± 26	
Symptom score	75.8 ± 21.2	
Quality of life score	66 ± 27.4	
Social limitation score	67.6 ± 28.4	

*Thirty-nine participants had successful cardiopulmonary stress testing.

†Twenty-two participants attained their ventilatory threshold.

‡Adjusted for body weight.

In univariate analysis, predictors of peak VO_2 (log [natural] transformed) assessed were age, race, serum 25OHD, RER, HF etiology, EF, BMI, and sex. There was statistically significant positive association of 25OHD with peak VO_2 (P = .05) (Figure 1). Predictors that reached the .1 level of significance in univariate analysis were included in multivariable regression analysis. Serum 25OHD maintained an independent relationship with peak VO_2 (Table III) (adjusted R^2 = 0.32). This model explained 32% of the

variability in peak VO 2. Based on this regression model, for every 5 ng/mL increase in serum 25OHD, the VO 2 increased by 4.6%.

Table III. Univariate and multivariable analysis for the log (natural) transformed peak Vo2 as the dependant variable

Univariate regression analysis			Multivariable regression analysis*	
Variable	**Estimate (95% CI)**	***P***	**Estimate (95% CI)**	***P***
Age	0.993 (0.985–1.001)	08	0.995 (0.987–1.004)	.26
Race†	1.169 (0.978–1.40)	08	1.107 (0.924–1.325)	.26
25OHD	1.009 (1.000–1.019)	05	1.009 (1.000–1.018)	.044
RER	3.258 (1.413–7.514)	007	2.614 (1.077–6.348)	.035
HF etiology‡	0.822 (0.662–0.991)	04	0.891 (0.747–1.061)	.188
EF	0.997 (0.991–1.004)	40	R^2 = 0.41, adjusted R^2 = 0.32	
BMI	0.994 (0.982–1.005)	31		
Sex§	0.918 (0.765–1.101)	35		

*Variables that reached $P \leq .1$ in univariate analysis were included in the multivariable analysis.

†Reference group includes AA.

‡Reference group includes ischemic.

§Reference group includes men.

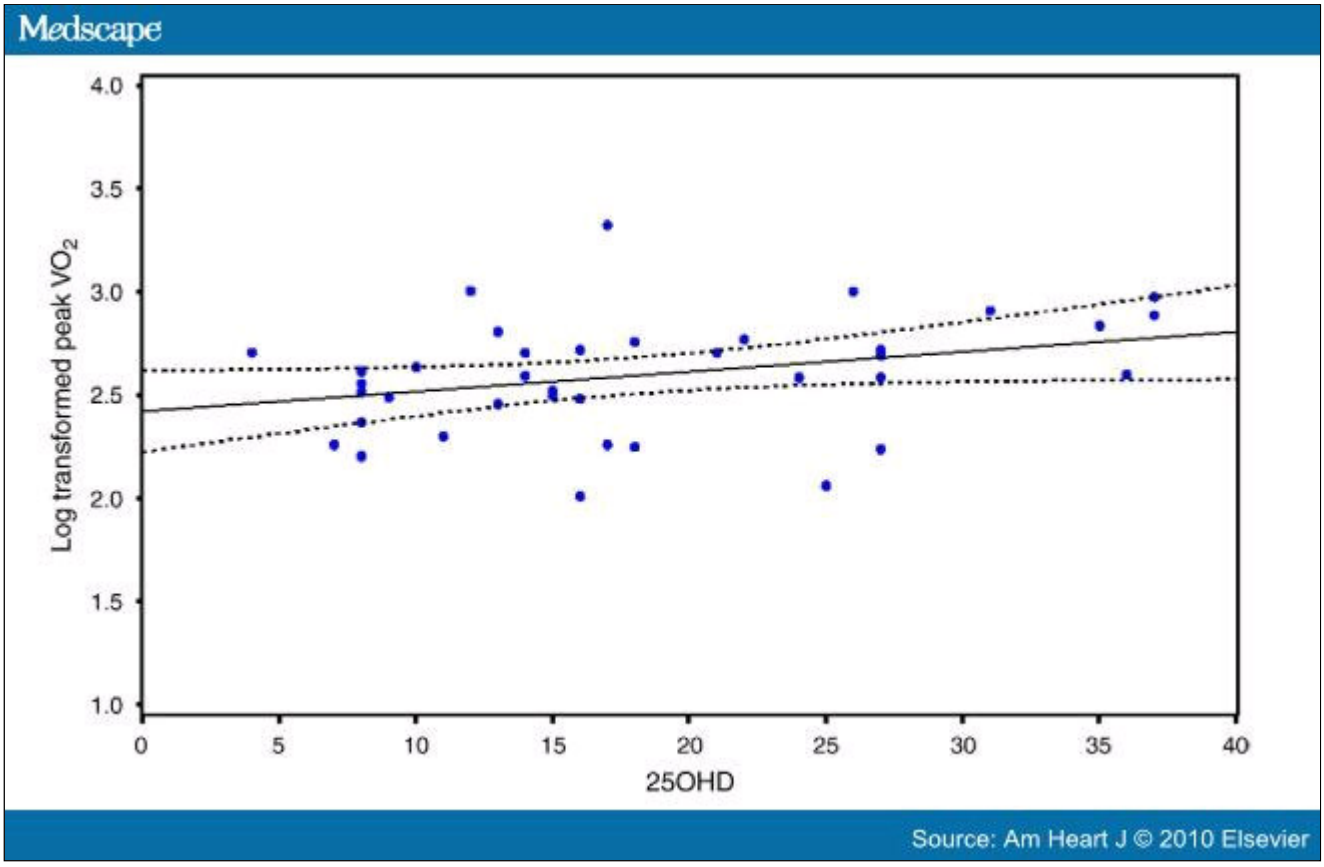

Figure 1. Univariate relationship between log transformed peak Vo_2 and 25OHD. Peak Vo_2 is back-transformed for interpretability.

From the KCCQ, serum 25OHD concentrations were correlated with the physical limitation score (r = 0.32, P = .04). Univariate regression analysis showed that the BMI, 25OHD, sex, race, NYHA class, and etiology of HF (ischemic or nonischemic) were associated with the KCCQ physical limitation score at a .1 level of significance and were therefore included in the multivariable regression model. In multivariable regression model, only race (AA having lower scores) and NYHA class (lower class with higher scores) remained significant (P = .01; P < 001; adjusted R^2 = 0.40). This model explained 40% of the variance in the KCCQ physical limitation score.

Measure of isokinetic muscle strength (peak torque adjusted for body weight in flexion) showed no association with serum 25OHD concentration. Older age trended toward significance at P = .08, with older age relating to lower peak torque. Univariate analysis of race, sex, EF, and 25OHD concentration were not significantly associated with peak torque.

Discussion

In a small group of older patients with HF, we found that serum 25OHD concentrations ≤37.5 ng/mL were associated with peak VO_2 as a measure of functional capacity but not with isokinetic muscle strength. In addition, the KCCQ physical limitation domain was associated with 25OHD concentrations only in univariate analysis. This relationship was lost with multivariable model. We have previously demonstrated an association between 25OHD concentrations with the 6-minute walk distance and frailty in a cohort of patients with HF.[16] This study expands that observation to include peak VO_2, the gold-standard measure of functional capacity. The relationship between VO_2 and 25OHD level was shown previously in patients with HF who were NYHA class III or IV and referred for cardiac transplantation.[22] This observed association expands what was seen previously in evaluating an older more heterogeneous population in sex and race, as well as HF severity.

The participants in this study had either systolic or preserved systolic HF with functional limitations measured by NYHA classification. We choose to be inclusive of both types of HF because both are equally disabling and have abnormal peak VO_2,[23] albeit systolic failure incurs a higher risk of mortality.[24] Including HF-preserved systolic function is important in studies of older adults because at least 50% of older patients will have preserved systolic function.[25] In addition, the interaction that vitamin D may have on the RAAS[13,26] would not be specific to the EF, in that both types of HF have RAAS activation.

In the patient with HF, 25OHD concentrations may be directly impacted by their exposure to sunlight. Patients with low VO_2 often have low-activity levels and therefore may spend less time out of doors exposed to UVB light. From this study, there is no way to know if having HF and low-physical activity/sun exposure is lowering the 25OHD level and uninvolved in the pathophysiology of HF or if 25OHD concentrations are directly involved in worsening the functional capacity. Laboratory work in vitamin D has demonstrated direct myocardial effects of vitamin D including regulation of extracellular matrix protein turnover, calcium flux and myocardial contractility, and antiproliferative and hypertrophic effects.[27] However, much of this work has been done with $1,25(OH)_2D$.

Our findings of lower concentration of 25OHD in the AA patients in this cohort are consistent with the National Health and Nutrition Examination Survey. The National Health and Nutrition Examination Survey report comparing 1988 with 2004 has noted that although concentrations of 25OHD are remaining constant in the general population overall, AAs are an at-risk subgroup in which serum 25OHD concentrations have become more deficient over time.[28] The predominance of AA participants in our cohort is important when examining the association of vitamin D with heart disease. Vitamin D deficiency has been implicated as having influence over the hypertensive patient, increasing risk for adverse cardiovascular outcome.[7] Furthermore, vitamin D deficiency may confer more risk for disease and cardiovascular mortality in AAs than in other racial groups.[29,30] This disparity indicates a considerable and reversible public health challenge that requires further evaluation in a diverse patient population.

The deficiency of vitamin D prompts the question of repletion. Improving function with vitamin D repletion was recently studied in a 20-week randomized, placebo-controlled trial of 105 patients with systolic HF, mean age 78.9 years, and selected for low 25OHD concentrations.[31] The mean baseline 25OHD concentration in the treatment group increased from 8.21 to 17.4 ng/mL with 2 oral doses of 100,000 IU of ergocalciferol (vitamin D_2) given at baseline and again at 10 weeks. The study failed to show a change in physical performance outcome measure of the 6-minute walk test. The 25OHD concentration achieved in this study is unlikely an adequate change in the 25OHD concentration to see a response in physical performance. Similarly, a lack of improvement in VO_2 was seen in a study of 123 adults with HF (83% men, race not reported) who were supplemented with 2,000 IU cholecalciferol.[32] The mean concentration of 25OHD achieved was 26 ng/mL; at this concentration, there was a reduction in PTH and inflammatory mediators indicating a physiologic effect, but this concentration may be too low to impact a change in functional capacity, which is noted by the authors. A drop in the concentration of PTH in and of itself may be beneficial to reduce cardiovascular risk, disease, and related mortality.[33,34] However, there was no relationship between PTH and reported outcomes in this study.

An adequate 25OHD concentration for improved physical function is between 16 and 38 ng/mL.[15] For reducing cardiovascular risk, there is evidence that the optimum level is >40 ng/mL.[35] Studies of other disease states including bone mineral density have found adequate 25OHD concentration to be approximately 30 ng/mL for physiologic benefit.[36] In addition, a review of physical performance in older adults with vitamin D supplementation found that studies that included calcium supplementation had a positive effect over studies that gave vitamin D alone.[37]

The measure of health status, the KCCQ, did not show a significant relationship with the 25OHD concentration except for the physical limitation subscale in univariate analysis. Clearly, the most powerful predictor of the physical limitation score is the functional class that is clinically appropriate and expected.[38] Race was also a significant predictor in the model. African-American

patients are also known to have worse physical function scores when health status is measured.[39,40] This finding requires further evaluation in older AA patients with HF.

There was no relationship with isokinetic muscle strength and 25OHD concentrations in patients with HF. This was unexpected in that vitamin D deficiency has known skeletal muscle effects with severe vitamin D deficiency characterized by proximal muscle weakness and pain. Particularly, older adults who are deficient in vitamin D have muscle weakness and decreased muscle mass and are prone to falls.[15,26,41] Poor physical performance represented by slowed walk time, decreased grip strength, and measures of frailty has been correlated with vitamin D deficiency in both HF and non-HF populations.[17,26,37] Because of the limits of cross-sectional study design, measures of muscle strength with vitamin D repletion in functionally limited patients is still warranted because the relationship between skeletal muscle and vitamin D is so well established.

Study Limitations

This study is limited by the cross-sectional design, and therefore, causality cannot be determined. Nonetheless, the results are hypothesis generating, and clinical trials of vitamin D therapy in HF should assess the response of functional capacity in the older adult. This study did not demonstrate a relationship between health status or muscle strength and the serum concentration of 25OHD. This may be due to the small sample size and includes a large variance making statistical significance less likely.

Clinical Implications

The results of this study add to a growing body of clinical evidence that vitamin D may have influence over the health of the cardiovascular system. This pilot study begins to draw together the better-known effect of vitamin D on the musculoskeletal system with emerging evidence of the relationship of vitamin D to the cardiovascular system. This study itself may not change clinical practice in patients with HF, but it is provocative and provides a basis for further research. Should these associations be directly related to causation, the repletion of vitamin D in the elderly population with HF could have a broad public health impact. Furthermore, recommendations to maintain adequate vitamin D status are important to multiple physiologic processes and, perhaps, to decrease the risk of cancer. Testing of vitamin D status and repletion should be considered as part of standard clinical practice.[42]

Conclusion

Patients with HF may have an increase vulnerability to vitamin D deficiency because of the disease process that effects cardiopulmonary reserve and skeletal muscle function. Although there was no evidence from this cross-sectional analysis that there is an association with isokinetic muscle strength and 25OHD concentrations, the association with peak VO_2 may indicate a more complicated relationship with the cardiovascular system.

References

1. Wilson JR, Rayos G, Yeoh TK, et al. Dissociation between exertional symptoms and circulatory function in patients with heart failure. Circulation 1995;92:47–53.
2. Coats AJ. The "muscle hypothesis" of chronic heart failure. J Mol Cell Cardiol 1996;28:2255–62.
3. Hulsmann M, Quittan M, Berger R, et al. Muscle strength as a predictor of long-term survival in severe congestive heart failure. Eur J Heart Fail 2004;6:101–7.
4. Kim DH, Sabour S, Sagar UN, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). AmJ Cardiol 2008;102:1540–4.

5. Giovannucci E, Liu Y, Hollis BW, et al. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80.
6. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 2008;168:1340–9.
7. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–11.
8. Miller RR, Hicks GE, Shardell MD, et al. Association of serum vitamin D levels with inflammatory response following hip fracture: the Baltimore Hip Studies. J Gerontol A Biol Sci Med Sci 2007;62:1402–6.
9. Van den Berghe G, Van Roosbroeck D, Vanhove P, et al. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab 2003;88:4623–32.
10. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
11. Kong J, Qiao G, Zhang Z, et al. Targeted vitamin D receptor expression in juxtaglomerular cells suppresses renin expression independent of parathyroid hormone and calcium. Kidney Int 2008;74:1577–81.
12. Li YC. Vitamin D regulation of the renin-angiotensin system. J Cell Biochem 2003;88:327–31.
13. Li YC, Kong J, Wei M, et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229–38.
14. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 2001;86:1633–7.
15. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lowerextremity function in both active and inactive persons aged N or = 60 y. Am J Clin Nutr 2004;80:752–8.
16. Boxer RS, Dauser DA, Walsh SJ, et al. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. J Am Geriatr Soc 2008;56:454–61.
17. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007;92:2058–65.
18. Weber KT, Kinasewitz GT, Janicki JS, et al. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213–23.
19. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
20. Borg G. Borg's perceived exertion and pain scale. Champaign, Illinois: Human Kinetics; 1998.
21. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–6.
22. Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med 1997;103:197–207.
23. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.
24. Smith GL, Masoudi FA, Vaccarino V, et al. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510–8.
25. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
26. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88:5766–72.

27. Pilz S, Tomaschitz A, Drechsler C, et al. Vitamin D deficiency and myocardial diseases. Mol Nutr Food Res 2010;54:1103–13.
28. Ginde AA, Liu MC, Camargo Jr CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med 2009;169:626–32.
29. Fiscella K, Franks P. Vitamin D, race, and cardiovascular mortality: findings from a national US sample. Ann Fam Med 2010;8:11–8.
30. Melamed ML, Astor B, Michos ED, et al. 25-Hydroxyvitamin D levels, race, and the progression of kidney disease. J Am Soc Nephrol 2009;20:2631–9.
31. Witham MD, Crighton LJ, Gillespie ND, et al. The effects of vitamin d supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. Circ Heart Fail 2010;3:195–201.
32. Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebocontrolled trial. Am J Clin Nutr 2006;83:754–9.
33. Hagstrom E, Hellman P, Larsson TE, et al. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation 2009;119:2765–71.
34. Pilz S, Tomaschitz A, Drechsler C, et al. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. Eur Heart J 2010;31:1591–8.
35. May H, Anderson JL, Lappe DL, et al. Stratifying cardiovascular risk by vitamin D levels: what are the optimal cutoffs. J Am Coll Cardiol 2010;55:A59.E563.
36. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28.
37. Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. J Am Geriatr Soc 2003;51:1219–26.
38. Heidenreich PA, Spertus JA, Jones PG, et al. Health status identifies heart failure outpatients at risk for hospitalization or death. J Am Coll Cardiol 2006;47:752–6.
39. Kaul P, Lytle BL, Spertus JA, et al. Influence of racial disparities in procedure use on functional status outcomes among patients with coronary artery disease. Circulation 2005;111:1284–90.
40. Spertus J, Safley D, Garg M, et al. The influence of race on health status outcomes one year after an acute coronary syndrome. J Am Coll Cardiol 2005;46:1838–44.
41. Houston DK, Cesari M, Ferrucci L, et al. Association between vitamin D status and physical performance: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2007;62:440–6.
42. Souberbielle JC, Body JJ, Lappe JM, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. Autoimmun Rev 2010.

Acknowledgements
The project described was supported by the Clinical and Translational Science Collaborative and utilized the REDCap database. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of National Center for Research Resources or National Institutes of Health.

American Heart Journal. 2010;160(5):893-899.