Can Vitamin D Supplementation Improve the Severity of Congestive Heart Failure?

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The aim of the present study was to investigate whether vitamin D supplementation could improve biochemical findings and functional capacity of patients with heart failure (HF). One hundred patients with New York Heart Association (NYHA) class I through III HF were included in this prospective study and their 25-hydroxyvitamin D levels were evaluated. Only 6% of the participants had a sufficient serum concentration of 25(OH) D >30 nmol/L. Patients with insufficient or deficient serum levels of 25 (OH) D (<30 ng/mL and <20 ng/mL, respectively) received oral vitamin D_3 (cholecalciferol) for a total period of 4 months. Vitamin D supplementation increased mean serum concentration of 25(OH) D from 12.63±7.60 nmol/L to 54.49±18.01 nmol/L (P<.001). After vitamin D supplementation, the serum level of pro-brain natriuretic peptide markedly decreased (P<.001). Cholecalciferol significantly decreased high-sensitivity C-reactive protein level (P<.001). Restoration of serum 25(OH) D level was also associated with substantial improvement in NYHA class (P<.001) and 6-minute walk distance (P<.001).

Heart failure (HF) is an increasingly prevalent health problem affecting more than 15 million of patients worldwide.[1] It is a major source of morbidity and mortality in elderly populations. It can be a debilitating syndrome that leads to significant functional limitations. Despite the advances in understanding the pathophysiology and treatment, it still has a poor prognosis.[2,3] Only 35% of patients will survive within 5 years of diagnosis.[2]

Vitamin D is a hormone that is necessary for bone and muscle health. However, it does not merely act on the calcium-phosphorus metabolism, and extraskeletal effects of vitamin D have been assumed.[4,5] Limited dietary intake or skin synthesis are two important factors contributing to vitamin D deficiency. In some reports, a prevalence as high as 50% of the US adult population are vitamin D deficient.[6,7] Vitamin D deficiency may be of particular importance in patients with HF, as a growing body of studies has found it to be more prevalent in patients with congestive HF. Accumulating evidence suggests that vitamin D deficiency in HF is not a negligible laboratory finding and there may be an intense association between these two common clinical entities.[8] It has been shown that patients with congestive HF (CHF) had 34% lower 25 (OH) D levels compared with controls.[8] In some studies, emphasis has been given to the possible causative role of vitamin D in HF. Moreover, it was hypothesized that in patients with HF, vitamin D supplementation may reduce disease progression and symptom severity through suppression of the renin-angiotensin- aldosterone system and parathyroid hormone, down-regulation of inflammatory mediators, suppression of cardiac remodeling, promotion of cell growth and differentiation, reduction of blood pressure, and improvement in muscle strength.[9–17] As a result, numbers of studies were designed to evaluate the beneficial or detrimental effects of vitamin D on HF. However, data are still lacking regarding the precise effects of vitamin D supplementation on laboratory parameters as well as functional capacities of HF patients. Therefore, the present study was designed to investigate whether vitamin D restoration could improve biochemical and functional parameters of CHF.

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MATERIALS AND METHODS

Participants

One hundred consecutive patients with the diagnosis of CHF according to the European Society of Cardiology guidelines[18] aged 15 years and older who presented to the Heart Failure and Transplant Clinic of Rajaei Cardiovascular, Medical and Research Center, a tertiary center for cardiovascular diseases in Tehran, Iran, during September 2010 and February 2012 were enrolled in this prospective study. All patients have been on optimal medical treatment of diuretics and neurohormonal blockers according to latest guidelines on HF management[19] for at least the 3

preceding months. Moreover, patients were kept on the same medical regimen (including the type and dose of the medications) during the study period. Patients were excluded if they had hypercalcemia; nephrolithiasis; sarcoidosis; hemotoneal or peritoneal dialysis and/or serum creatinine concentration of >2 mg/dL; myocardial infarction in the preceding 6 months; and intake of supplements containing vitamin D and/or calcium, corticosteroids, parathyroid hormone (PTH), androgen, or estrogen. Patients with New York Heart Association (NYHA) class IV and patients with any exacerbations of HF symptoms during the last 3 months were also excluded.

The study was reviewed and approved by the institutional review board at the Tehran University of Medical Sciences and written informed consent was obtained from all participants. It should be noted that the present study complies with the Declaration of Helsinki.

Cardiac Examination

The severity of HF was assessed by a throughout physical examination. The NYHA function class of all patients was determined by the same investigator by evaluating each patient at rest, dressing, walking, and climbing the stairs. NYHA scores range from I (no symptoms of HF) to IV (symptoms at rest).[20]

Physical Performance Assessment

Physical performance of patients was assessed using the 6-minute walk test (6MWT) according to the protocol of Guyatt and colleagues.[21]

Biochemical Measurements

Blood samples were collected in the morning after an overnight fast and immediately processed on the same day. Serum calcium and phosphorus were measured by colorimetric method. PTH was measured using immunoassay (Immulite 1000; Siemens Medical Solutions Diagnostics, Los Angeles, CA) with an average intra-assay variability of 3.2%. Serum 25 (OH) D concentration was by enzyme immunoassay (DiaSorin, Saluggia (Vercelli), Italy). The intra-assay and inter-assay coefficients of variations (CVs) were 4.5% and 8.5%, respectively. Serum pro–brain natriuretic peptide (proBNP) levels were determined by enzyme immunoassay (Siemens Healthcare Diagnostic Inc, Elkhart, IN), with intra-assay and inter-assay CVs of 6% and 7.7%, respectively. Participants were classified into 3 categories on the basis of serum 25 (OH) D levels. Patients with 25 (OH) D levels of >30 ng/mL were classified as "normal," while levels of 20 to 29.9 ng/mL were considered "insufficient," and levels of <20 ng/mL were "deficient."

Echocardiographic Examination

All echocardiographic data were obtained and processed by the same echocardiographist. Echocardiography was performed using a Vivid 7 device (GE Medical System, Milwaukee, WI) with a 3-MHz variable frequency harmonic phased array transducer. Measurement of left ventricular end-diastolic dimension (EDD) was performed at the parasternal long-axis view by M-mode echocardiography. Left ventricular end-systolic volume (ESV) and left ventricular ejection fraction (EF) were measured by modified Simpson's method.

Vitamin D Supplementation

Patients with insufficient or deficient levels of 25 (OH) D were administered oral vitamin D3 (cholecalciferol) for a period of 4 months. The treatment regimen included 50,000 IU every week for 8 consecutive weeks followed by 50,000 IU every month for 2 consecutive months. Afterward, all patients, including those with normal baseline 25 (OH) D, were assessed again.

Statistical Analysis

All analyses were conducted by Statistical Package for Social Sciences software, version 19 (SPSS Inc, Chicago, IL). All data were initially analyzed using the Kolmogorov-Smirnov test to assess for normality. Categorical variables are presented as numbers and percentages and quantitative variables as mean±standard deviation. Categorical data were compared by chi-square test and quantitative variables by Student *t* test, Mann-Whitney test, the Kruskal-Wallis test, as appropriate. For comparative analysis of quantitative variables between vitamin D subgroups or NYHA functional classes, one-way ANOVA was used. Relationships were assessed using Pearson, Spearman, or Kendall tests depending on their distribution. Changes in all of the outcome measures were normally distributed and were analyzed using 2-sample Student *t* test. All *P* values were two-tailed and $P<.05$ was considered statistically significant.

RESULTS

Patient Characteristics

One hundred patients, including 73 (73%) men and 27 (27%) women, were enrolled in the study. The mean age of the cohort was 45.25±15.53 years. The demographic characteristics of the patients are shown in Table I.

Cardiac Characteristics

Nonischemic cardiomyopathy (73%) was the main cause of CHF in our study population. At the time of clinical evaluation, the percentages of NYHA class I, II, and III were 3%, 45%, and 52%, respectively.

Physical Performance Characteristics

Table II shows the physical performance characteristics of the study group. The mean 6MWT was 361±77 m. Subgroups of 25 (OH) D did not significantly differ among the different NYHA class groups

TABLE I. Demographics of the Study Population

Characteristic	Value
Age, y	45.25±15.53
Sex (female/male)	23 (23)/73 (73)
BSA, m^2	1.78±0.14
NYHA class	
I	3 (3)
II	43 (43)
III	54 (54)
Etiology of heart failure	
Ischemic	27 (27)
Valvular	18 (18)
Cardiomyopathy	55 (55)
Heart failure pharmacotherapy	
Diuretic	89 (89)
ACE inhibitor or ARB	95 (95)
β-Blocker	93 (93)
Spironolactone	83 (83)
Digoxin	61 (61)
CRT	10 (10)
ICD	11 (11)
VAD	0
Comorbid conditions	
Hypertension	26 (26)
Diabetes	31 (31)
Dyslipidemia	9 (9)
Chronic renal failure	8 (8)
Chronic liver disease	3 (3)
Current smoking	17 (17)
Heart rate, beats per min	73±12
SBP, mm Hg	112.47±14.72
DBP, mm Hg	73.84±10.19

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BSA, body surface area; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; VAD, ventricular assist device. Data are presented as number (percentage) and mean±standard deviation.

TABLE II. Baseline Physical Performance Characteristics of the Study Population According to 25 (OH) D Concentrations

	All	Normal	Insufficient	Deficient	*P* Value
NYHA class, No.					
I	3 (3)	1 (1)	0	2 (2)	.22
II	45 (45)	3 (3)	10 (10)	32 (32)	
III	52 (52)	2 (2)	8 (8)	42 (42)	
6MWT, m	361±77	394±61	353±62	360±81	.48

Abbreviations: NYHA, New York Heart Association; 6MWT, six-minute walk test.
Data are presented as number (percentage) and mean±standard deviation.

(*P*=.22); neither was correlated with NYHA class (*r*=0.12, *P*=.21). NYHA class was significantly correlated with 6MWT (*r*=0.32, *P*=.001). The baseline 6MWT was not significantly different among CHF patients with various vitamin D profiles (mean values: 394±61 m for the normal group, 353±62 m for the insufficient group, and 360±81 m for the deficient group; *P*=.48).

Biochemical Characteristics

The biochemical characteristics of the study participants according to 25 (OH) D subgroups are illustrated in Table III. Among 100 CHF patients, 76% had vitamin D insufficiency or deficiency at the time of enrollment. Only 6% of the participants in the study had a sufficient serum concentration of 25 (OH) D >30 nmol/L. Serum PTH was significantly correlated with 25 (OH) D (*r*=0.21, *P*=.03). No significant differences were present regarding the frequency of 25 (OH) D subgroups or concentrations of 25 (OH) D, calcium, phosphorus, and proBNP in men and women (all *P*>.05). A significant correlation was seen between the NYHA functional class and serum level of proBNP (*r*=0.37, *P*<.001). Serum calcium level was inversely correlated with proBNP (*r*=−0.22, *P*=.02) (Figure 1).

High-sensitivity C-reactive protein (hs-CRP) was correlated with serum proBNP level (*r*=0.22, *P*=.02). Serum level of proBNP was also inversely associated with 6MWT (*r*=−0.27, *P*=.005). ProBNP and 6MWT were significantly different among CHF patients with NYHA class I to III (both *P*<.001).

Associations of Vitamin D With HF

It is worth noting that the differences of mean serum concentrations of hs-CRP among patients with various 25 (OH) D subgroups were inconspicuous (*P*=.11). The concentrations of proBNP were not significantly different among CHF patients with various vitamin D profiles (mean values: 1125.16 ng/L for patients with normal 25 (OH) D level, 2718 ng/L for patients with insufficient 25 (OH) D level, and 2626.80 ng/L for patients with deficiency of 25 (OH) D level; *P*=.08). Furthermore, baseline 25 (OH) D had no significant association with NYHA functional class, proBNP level, or 6MWT at the time of enrollment to the study (all *P*>.05).

Associations of PTH With HF

The baseline serum PTH level was significantly associated with higher NYHA class and serum proBNP level (*r*=0.20, *P*=.04 and *r*=0.28, *P*=.004, respectively). Moreover, the baseline serum PTH level was negatively correlated with 6MWT (*r*=−0.31, *P*=.001) (Figure 2). Hyperparathyroidism (PTH >87 ng/L) was associated with higher NYHA functional class (*r*=0.23, *P*=.01).

Effects of Vitamin D Supplementation

After supplementation in patients with insufficient or deficient levels of 25 (OH) D, mean concentration of 25 (OH) D increased by 41.86 nmol/L. Vitamin D supplementation decreased mean serum PTH concentrations by 36.73 ng/L. Moreover, a 1.44-mg/dL decrease in mean serum calcium along with a

TABLE III. Biochemical Characteristics of the Study Population According to 25(OH) D Concentrations

	All	Normal (n=6)	Insufficient (n=18)	Deficient (n=76)	*P* Value
PTH, ng/L	106.89±65.14	62.76±18.19	91.69±42.19	113.97±70.10	.04[a]
Ca, mg/dL	9.60±0.59	9.80±0.67	9.81±0.56	9.53±0.58	.11
Ph, mg/dL	4.01±0.62	4.05±0.76	4.23±0.47	3.95±0.64	.07
25(OH) D, nmol/L	14.35±10.68	41.33±15.95	25.33±2.39	9.64±4.72	<.001[a]
hs-CRP, mg/dL	14.35±10.68	24.20±14.87	15.88±17.89	17.08±13.65	.11

Abbreviations; Ca, calcium; hs-CRP, high-sensitivity C reactive protein; Ph, phosphorus; PTH, parathyroid hormone.
Data are presented as mean±standard deviation.
[a]Statistically significant.

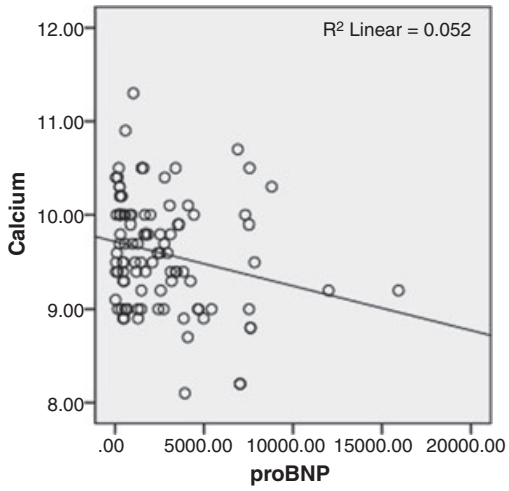

FIGURE 1. Baseline pro–brain natriuretic peptide (proBNP) and calcium levels were inversely correlated (r=−0.22, P=.02).

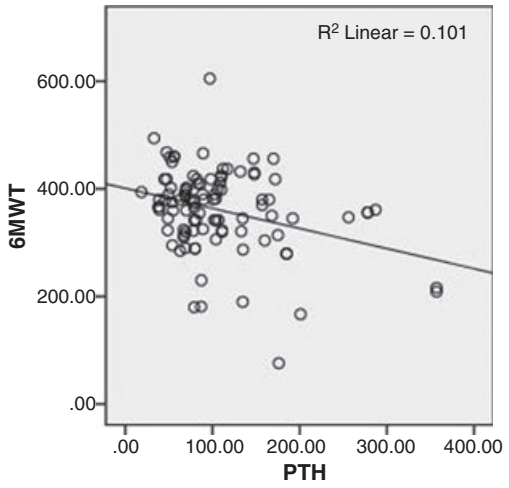

FIGURE 2. Baseline parathyroid hormone (PTH) was negatively correlated with six-minute walk test (6MWT) (r=−0.31, P=.001).

0.13-mg/dL increase in mean serum phosphorus levels was seen. All of these changes in biochemical parameters, including 25(OH) D, calcium, phosphate, and parathyroid hormone were considered statistically significant (all P<.001). During 12 weeks of medical treatment with vitamin D, mean NYHA functional class in the study population improved significantly (P<.001).

Furthermore, a reduction of 827.32 pg/mL was seen in the mean serum concentration of proBNP hormone (P<.001). Vitamin D supplementation also significantly improved 6MWT (P<.001). Compared with baseline values, a statistically significant decline was seen in serum level of hs-CRP, an inflammatory marker in HF (P<.001). Comprehensive data regarding the changes in the aforementioned variables is provided in Table IV. Vitamin D supplementation also improved a number of echocardiographic measures, as shown in Table IV.

Patients With Sufficient Baseline Serum Level of 25 (OH) Vitamin D

Data for the untreated group are depicted in Table V and it is noteworthy to mention that this "vitamin D sufficient" group was so small in number (6 patients) that the results could not be brought up as a comparison to the treated group. However, considering the standard "neurohormonal blockade escalation" strategy (uptitration of β-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists) in this untreated group, their merely unchanged clinical status might be of importance.

Safety Measures

None of the participants in the study experienced an increase in serum creatinine >50% from baseline. Moreover, none of the patients exhibited clinical features of vitamin D intoxication during the study period. Hypercalcemia was mild and asymptomatic in all detected cases and did not result in the need for discontinuation of therapy.

DISCUSSION

This is one of few studies, at least to our knowledge, that evaluated the efficacy of vitamin D supplementation in an HF population. The main finding of the current investigation is that 12 weeks of administration of oral vitamin D_3 to HF patients with insufficient or deficient levels of serum vitamin D markedly improves their physical performance and the laboratory parameters of HF.

TABLE IV. Effects of Vitamin D Supplementation on Biochemical, Functional, and Echocardiographic Parameters in Patients With Insufficient or Deficient Levels of 25 (OH) D

	Insufficient and Deficient (n=94)			Insufficient (n=18)			Deficient (n=76)			
	Before	After	*P* Value	Before	After	*P* Value	Before	After	*P* Value	Changes in Insufficient vs Deficient *P* Value
25 (OH) D, nmol/L	12.63±7.60	54.49±18.01	<.001[a]	25.35±2.39	55.77±12.29	<.001[a]	9.64±4.72	54.20±19.18	<.001[a]	.006[a]
PTH, ng/L	105.45±63.82	68.72±38.69	<.001[a]	91.69±42.19	68.42±12.37	.10	113.97±70.10	68.79±42.68	<.001[a]	.41
Ca, mg/dL	9.61±0.56	8.17±3.31	<.001[a]	9.81±0.56	7.42±4.10	.02[a]	9.53±0.58	8.34±3.11	<.001[a]	.26
Ph, mg/dL	4.03±0.63	4.16±0.39	<.001[a]	4.23±0.47	4.07±0.28	.01[a]	3.95±0.64	4.18±0.42	.18	.06
hs-CRP, mg/dL	16.85±14.45	11.34±9.45	<.001[a]	15.88±11.89	11.25±10.79	.26	17.08±13.65	11.36±9.18	<.001[a]	.75
proBNP, pg/mL	2508.60±1867.99	1681.28±1181.68	<.001[a]	2718.00±2224.36	1295.92±1060.43	.002[*]	2626.47±1913.29	1772.55±1367.09	<.001[a]	.14
6MWT, m	363±77	393±88	<.001[a]	353±62	405±58	.002[a]	360±81	390±93	.003[a]	.22
NYHA	2.50±0.56	2.02±0.71	<.001[a]	2.44±0.51	1.66±0.59	<.001[a]	2.51±0.57	2.10±0.72	<.001[a]	.03[*]
EF	19.94±9.57	23.02±9.67	<.001[a]	21.94±9.41	24.61±8.83	.06	19.47±9.61	22.64±9.88	<.001[a]	.90
ESV	144.36±58.15	139.11±55.84	<.001[a]	125.01±46.26	121.61±47.89	.21	148.94±59.97	143.26±57.06	.004[a]	.42
EDD	6.47±0.86	6.26±0.82	.002[a]	6.49±0.94	6.29±0.93	.09	6.46±0.85	6.26±0.80	<.001[a]	.38
E/E_m	11.77±3.86	9.36±2.62	<.001[a]	12.66±4.86	9.85±3.61	.002[a]	11.56±3.58	9.25±2.34	<.001[a]	.52

Abbreviations: Ca, calcium; E/E_m, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; EDD, end-diastolic dimension; EF, ejection fraction; ESV, end-systolic volume; hs-CRP, high-sensitivity C-reactive protein; NYHA, New York Heart Association; Ph, phosphorus; proBNP, pro–brain natriuretic peptide; PTH, parathyroid hormone; 6MWT, six-minute walk test.
Data are presented as number (percentage) and mean±standard deviation.
[a]Statistically significant.

TABLE V. The Changes in Biochemical, Functional and Echocardiographic Parameters in Patients With Sufficient Levels of 25 (OH) D During the Study Period

	Sufficient (n=6)		
	Baseline	After 4 Months[a]	*P* Value
25 (OH) D, nmol/L	41.33±15.95	47.72±13.82	.79
PTH, ng/L	62.76±18.19	69.62±13.27	.87
Ca, mg/dL	9.80±0.67	9.69±0.82	.48
Ph, mg/dL	4.05±0.76	4.03±0.72	.82
hs-CRP, mg/dL	24.20±14.87	20.09±12.03	.07
proBNP, pg/mL	1125.16±696.62	1022.82±726.82	.36
6MWT, m	394±61	407±72	.42
NYHA	2.16±0.75	1.83±0.75	.17
EF	21.66±13.66	23.02±10.74	.81
ESV	103.33±32.21	139.11±29.46	.62
EDD	5.86±0.62	6.26±0.46	.17
E/E_m	9.66±2.58	9.36±1.83	.78

Abbreviations: Ca, calcium; E/E_m, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; EDD, end-diastolic dimension; EF, ejection fraction; ESV, end-systolic volume; NYHA, New York Heart Association; Ph, phosphorus; proBNP, pro–brain natriuretic peptide; 6MWT, 6-minute walk test.
Data are presented as mean±standard deviation.
[a]It should be noted that patients with sufficient serum level of 25 (OH) D (shown in this table) had not been taking vitamin D supplementation.

In previous studies it has been shown that restoration of serum vitamin D improves muscle strength and walking distance.[13] However, little was known regarding the effects of vitamin D therapy on 6-minute walk distance in the HF population. In our study, vitamin D supplementation caused an improvement in exercise capacity of patients with HF, reflected as prolongation of 6MWT. This is in contrast to the previous report by Witham and colleagues,[22] which showed that a regimen of 100,000 IU of ergocalciferol at 0 and 10 weeks did not significantly improve the 6-minute walk distance in 53 elderly patients with systolic HF.

A prospective double-blind randomized trial was conducted by Schleithoff and colleagues[23] in 123 HF patients with NYHA class >II. They randomly assigned younger patients with HF to receive either a combination of vitamin D_3 (cholecalciferol) at a dose of 2000 IU daily and calcium (500 mg daily) or calcium and placebo. After 9 months they assessed inflammatory cytokines, echocardiographic parameters, and overall survival. Their results showed that patients who received vitamin D did not show a significant reduction in tumor necrosis factor α (TNF-α). Although, in the patients treated with calcium alone, a significant (12% from baseline value) increase was seen in the concentration of TNF-α. On the other hand, interleukin 10 concentrations increased by 43% in the group treated with vitamin D while it did not change significantly in the other group. The results of this study shed light on the possible role of vitamin D

supplementation in the reduction of the inflammatory state in patients with HF. Their findings also support the results of our investigation, which revealed that vitamin D therapy may suppress the inflammation process in HF, measured by hs-CRP. Although, Schleithoff and colleagues[23] showed that the changes in CRP had no significant difference between patients treated with or without vitamin D. The significance of this controversy is questionable, however, and further investigations are needed to clarify the possible anti-inflammatory effects of vitamin D supplementation in HF.

Our results showed that vitamin D supplementation in HF patients led to a significant decline in the plasma concentration of proBNP. This finding concurs with the previous reports by Witham and colleagues[22] in the study described above, which revealed a substantial fall in BNP level after 10 weeks of therapy with oral vitamin D2 supplementation. However, Schleithoff and colleagues[23] believed that vitamin D supplementation could not significantly affect serum concentrations of natriuretic peptides.

It is also noteworthy that Witham and colleagues[22] tried a 2-bolus administration of 100,000 U of ergocalciferol in contrast to the weekly regimen we applied, which might provide patients with more steady serum levels of vitamin D. Although Witham and colleagues believed that their treatment strategy would induce more than a 100% rise in 25-hydroxyvitamin D level at 10 weeks with a sustained level at 20 weeks, they failed to increase the average concentration of post-supplementation 25 (OH) D level to the sufficient level. Moreover, their study was conducted on the elderly population. As proposed by Levitan and Judd,[24] vitamin D treatment may have unremarkable effects on HF in older patients. On the other hand, in the study by Schleithoff and colleagues,[23] a concomitant supplementation of calcium was also carried out. It has been previously postulated that calcium treatment may adversely affect the vascular health independent of vitamin D supplementation.[25]

It has been shown previously that low circulating 25 (OH) D is associated with left ventricular dilation and reduced function. Ameri and colleagues[26] showed that patients with serum 25 (OH) D level <25 nmol/L had significantly higher left ventricular dimensions and volumes, as compared with patients with a 25 (OH) D level >25 nmol/L. However, because of the small number of patients with sufficient baseline vitamin D level (n=6), we could not make a comparison between our study groups in this regard. Other important finding of our study is that vitamin D therapy may affect ventricular function in a favorable pattern. We showed that patients with depleted serum 25 (OH) D levels had a significant increase in left ventricular EF after 4 months of vitamin D supplementation. The effect of vitamin D therapy on left ventricular ESV was also remarkable. Moreover, left ventricular end-diastolic dimension and E/Em were also notably altered toward favorable "reverse remodeling." This may explain the rationale of the improvements in the clinical and functional parameters of HF after vitamin D supplementation. However, establishing the significance of these findings merits further studies with more detailed echocardiographic indices, which could confidently elucidate the effects of vitamin D on geometry and function of the failing hearts.

STUDY LIMITATIONS

There are several important strengths of this study. Firstly, using the described regimen for vitamin D supplementation, we could raise the average concentration of the vitamin D level in our study population to the optimum level. After supplementation, none of the patients had deficient levels of 25 (OH) D. It has been demonstrated that serum 25 (OH) D concentrations of >33 ng/mL and <90 ng/mL (80–225 nmol/L) may be adequate to restore vitamin D–dependent functions.[27–30] Secondly, the present study included a younger study population and any intervention during the first years of the disease course may have more beneficial effects. Thirdly, we used vitamin D_3 (cholecalciferol), which has a longer half-life and also results in greater peak levels of vitamin D.[29]

The major limitations of the present study are the relatively small sample size and the lack of an arm of a placebo-treated control group. Results should be evaluated in comparison to a control group to minimize the effects of overlooked confounders.

CONCLUSIONS

The results of our study indicate that an appropriate strategy of vitamin D supplementation decreases the severity of HF, reflected in the reduction of serum proBNP. We also demonstrated that vitamin D causes a pronounced improvement in physical capacity of patients. Moreover, vitamin D was able to suppress the concentration of hs-CRP. Our data provide valuable evidence for the efficacy of vitamin D supplementation in the optimal management of HF.

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References

1 Young JB. The global epidemiology of heart failure. *Med Clin North Am*. 2004;88:1135–1143.
2 Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25:1614–1619.
3 Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397–1402.
4 Barnard K, Colón-Emeric C. Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition. *Am J Geriatr Pharmacother*. 2010;8:4–33.
5 Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest*. 2005;35:290–304.
6 Lee JH, O'Keefe JH, Bell D, et al. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol*. 2008;52:1949–1956.

7 Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2007;167:1159–1165.
8 Zittermann A, Schleithoff SS, Tenderich G, et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol*. 2003;41:105–112.
9 Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev*. 2006;11:25–33.
10 Coratelli P, Petrarulo F, Buongiorno E, et al. Improvement in left ventricular function during treatment of hemodialysis patients with 25-OHD3. *Contrib Nephrol*. 1984;41:433–437.
11 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;62:1402–1406.
12 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;88:4623–4632.
13 Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
14 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;74:1577–1581.
15 Li YC. Vitamin D regulation of the renin-angiotensin system. *J Cell Biochem*. 2003;88:327–331.
16 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;110:229–238.
17 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;86:1633–1637.
18 Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388–2442.
19 Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010;16:e1–e194.
20 Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. *Eur Heart J*. 2008;29: 2388e442.
21 Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J*. 1985;132:919–923.
22 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.
23 Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83:754–759.
24 Levitan EB, Judd SE. Can vitamin D supplementation improve physical function and quality of life in older patients with heart failure? *Circ Heart Fail*. 2010;3:183–184.
25 Sabbagh Z, Vatanparast H. Is calcium supplementation a risk factor for cardiovascular diseases in older women? *Nutr Rev*. 2009;67:105–108.
26 Ameri P, Ronco D, Casu M, et al. High prevalence of vitamin D deficiency and its association with left ventricular dilation: an echocardiography study in elderly patients with chronic heart failure. *Nutr Metab Cardiovasc Dis*. 2010;20:633–640.
27 Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr J*. 2004;3:8.
28 Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999;69:842–856.
29 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nut*. 2003;89:552–572.
30 Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. *Altern Med Rev*. 2005;10:94–111.