



## The effect of vitamin D therapy in the improvement of cardiac performance and exercise capacity in patients with heart failure: A double-blind, randomized, placebo-controlled trial

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### Original Article

#### Abstract

**BACKGROUND:** Low vitamin D status may contribute to the pathogenesis of heart failure (HF), but therapeutic roles of vitamin D on cardiac performance are not well known. We evaluated vitamin D effects on left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class in patients with HF for the first time.

**METHODS:** This study was a double-blind, randomized, placebo-controlled trial. 110 patients with HF admitted to Shahid Chamran and Khorshid Hospitals, Isfahan, Iran, randomly received 500 mg calcium daily plus either 50000 IU vitamin D<sub>3</sub> per week (case group) or placebo (control group) for 6 months. Biochemical variables, LVEF, and NYHA functional class were assessed at baseline and after 6 months.

**RESULTS:** 81 patients completed the study. Vitamin D supplementation increased mean serum 25-hydroxyvitamin D [25(OH)D] concentration in the case group by 33.9 ng/ml ( $P < 0.001$ ). After 6 months of treatment, both groups showed improvement in LVEF, but the extent of improvement was significant only in the case group (5.48% versus 0.44%,  $P < 0.001$ ). The NYHA functional class improved in the case group but remained constant in the control group ( $P < 0.001$ ).

**CONCLUSION:** Vitamin D<sub>3</sub> improved LVEF and NYHA functional class in patients with HF and might serve as a new agent for the future treatment of this disease.

**Keywords:** Heart Failure; Vitamin D; Randomized Controlled Trial

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#### Introduction

Heart failure (HF) is a chronic disease, with worldwide increasing prevalence, especially in elderly people.<sup>1-4</sup> Despite recent advances in management, HF so far carries an unacceptably high mortality rate.<sup>5,6</sup> Patients with HF, especially elderly people, are prone to nutritional problems.<sup>7,8</sup> Reduced mobility may lead to reduced exposure to sunlight and therefore vitamin D synthesis. These patients have considerably lower concentrations of vitamin D metabolites, 25-hydroxyvitamin D [25(OH)D] and its activated form, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] or calcitriol, than the age-matched healthy controls.<sup>9-11</sup>

There are several physiologic links between vitamin D and cardiac function. Vitamin D receptor (VDR) exists in a large number of different cell types among them cardiomyocytes, vascular endothelial cells, neurons, and immune cells.<sup>10,12,13</sup>

Calcitriol is an important regulator of calcium metabolism known as a regulator of intracellular calcium in various tissues and cellular cytokine secretion.<sup>10,12,14</sup> Now, calcitriol plays an important role which has been realized recently. In cardiac muscle cells, a calcitriol-dependent calcium (Ca<sup>++</sup>)-binding protein and calcitriol-mediated rapid activation of voltage-dependent Ca<sup>++</sup> channels exist.<sup>15,16</sup> This indicates that calcitriol plays a pivotal role in the regulation of myocardial contractility.

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Additional evidence emphasizing the role of vitamin D deficiency in the pathogenesis of HF comes from the mice, in which VDR was genetically disrupted. Impairment of VDR in these mice resulted in over-stimulation of the renin-angiotensin system (RAS), the elevation of blood pressure, increasing concentrations of the atrial natriuretic peptide (ANP), and cardiac hypertrophy.<sup>17</sup>

Although low vitamin D status may contribute to the pathogenesis of HF, the effects of vitamin D therapy on cardiac performance are not well known. The aim of the present study was to assess, for the first time, the efficacy of therapeutic doses of vitamin D on left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class of patients with HF.

## Materials and Methods

**Study design:** This double-blind, randomized, placebo-controlled study was performed from October 2007 until August 2008. The study was registered and approved at the Iranian Registry of Clinical Trials (IRCT138706121181N1). After approval of the study by the Ethics Committee of the Chancellor of Research of Isfahan University of Medical Sciences, Isfahan, Iran, and obtaining written consent, patients with HF referred to cardiology clinic of Shahid Chamran and Khorshid Hospitals in Isfahan for evaluation and management were invited to participate in this study.

**Participants:** This study was performed in Shahid Chamran and Khorshid Hospitals, in 2007-2008. The inclusion criteria were as follows: providing informed written consent, being ambulatory, NYHA functional class  $\leq$  III, and LVEF  $\leq$  45%. The exclusion criteria were: untreated hypercalcemia, current or recent nephrolithiasis, intake of supplements containing calcium or vitamin D in recent three months, intake of corticosteroids or anticonvulsants, and serum creatinine concentration  $>$  2 mg/dl.

**Interventions:** The intervention group received a pearl containing 50000 IU of vitamin D<sub>3</sub> (Zahravi, Iran) per week and the control group received the placebo (an exactly similar pearl containing olive oil) for six months. Moreover, as the usual dietary calcium intake was less than recommended daily allowance, participants of both groups received a daily supplement of 500 mg calcium carbonate to improve calcium intake and also to simplify the evaluation of vitamin D effects independent of calcium.

**Outcomes:** The primary endpoints of the study were LVEF and NYHA functional class. At the

baseline visit and at the end of the study, we performed transthoracic echocardiography (TTE) to evaluate LVEF and also obtained blood samples for the assessment of calcium, phosphorus, albumin, 25(OH)D<sub>3</sub>, creatinine, and serum parathyroid hormone (PTH) concentration. We used a Vingmed 800 CF system for TTE and assessed LVEF by Biplane Simpson Method. Exercise capacity was assessed by a questionnaire and reported based on NYHA functional classification.<sup>18</sup>

We obtained blood samples of the participants from the antecubital vein, after a 12-hour fast. After centrifugation at room temperature for 10 minutes, serum samples were extracted, frozen, and stored at  $-20$  °C until analysis.

We measured 25(OH)D<sub>3</sub> by chemiluminescent immunoassay (CLIA) (DiaSorin Inc., Stillwater, MN, USA). The PTH (reference range: 16-65 pg/ml) was measured by radioimmunoassay (RIA) [immunoradiometric assay (IRMA), Immunotech (Beckman Coulter, Czech Republic)]. Serum calcium concentration was assessed by the use of the colorimetric method (Darman Kave, Isfahan, Iran). Albumin, phosphorous, and creatinine were also measured by colorimetric method (Pars Azmun, Karaj, Iran).

**Sample size:** The sample size was calculated using the following formula. A sample size of 36 was calculated for each group.

$$n = \frac{2(z_{1-\alpha/2} + Z_{1-\beta})^2 \times (S_1^2 + S_2^2)}{(m_1 - m_2)^2}$$

$$\alpha = 0/05 \rightarrow Z_{1-\alpha/2} = 1/96$$

$$\beta = 0/2 \rightarrow Z_{1-\beta} = 0/84$$

$$n = \frac{2 \times (1/96 + 0/84)^2 \times [(7/1)^2 + (7/2)^2]}{(26/2 - 30/9)^2} = 36$$

$$S_1 = 7.1, S_2 = 7.2$$

$$M_1 = 30.9, M_2 = 26.2$$

**Randomization and blinding:** After obtaining informed consent from the participants, they were randomly (by computer-generated random number lists) assigned to the intervention (case) and control groups. Each patient, depending on the pre-defined group, received a code and all other procedures or evaluations were based on the specified code. Only the final analysis was performed by unmasking the code. Therefore, both the participants and the research group were blinded to the grouping of the patients.

**Statistical methods:** Statistical data were analyzed by SPSS software (version 15, SPSS Inc., Chicago, IL, USA). Categorical variables were presented as

number and percentage. They were compared between groups using the chi-square ( $\chi^2$ ) test. Function class was reported as above and was compared between groups using Mann-Whitney test and within groups by Wilcoxon test. The normal distribution of parameters was assessed by Kolmogorov-Smirnov test (K-S test). LVEF and other parametric variables were presented as mean  $\pm$  standard deviation (SD). These variables and the extent of their changes from baseline were compared between groups using student's t-test and within groups (before and after treatment) by paired t-test.

## Results

**Baseline data:** 110 patients with HF (77 men and 33 women) entered the study. 81 patients completed the study (39 in the case and 42 in the control groups). The baseline characteristics of the participants are presented in table 1. There was no significant difference regarding baseline characteristics between the two groups. 10 patients from the case group and 8 patients from the control group did not complete the study. 5 patients died during the study and until two more following months (2 in the control and 3 in the case groups). There was no significant difference in the survival rate in the case and the control groups (95.6% and 97.0%, respectively,  $P = 0.673$ ). 3 patients could not complete the study because of deterioration in the health status [one patient developed pulmonary thromboembolism (PTE), one patient because of stroke, and the other one had decompensated HF]. 3 patients were excluded from the study, because they needed invasive interventional treatments for

ischemic heart disease (IHD) (one patient underwent coronary bypass surgery and two of them received coronary stent). Figure 1 shows a Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study process.

**Outcomes:** Baseline 25(OH)D<sub>3</sub> concentration in both groups was in the range of hypovitaminosis D.<sup>19</sup> The prevalence of low vitamin D status in participants was 83.6% (85.3% in controls vs. 81.8% in the case group,  $P = 0.700$ ). The mean serum vitamin D<sub>3</sub> concentration was  $22.7 \pm 21.1$  ng/ml.

At the end of the study, there was a significant elevation of serum concentration of 25(OH)D<sub>3</sub> in the case group ( $22.85 \pm 19.97$  versus  $55.40 \pm 31.53$  ng/ml,  $P < 0.001$ ). In the control group, 25(OH)D<sub>3</sub> increased from  $22.46 \pm 22.28$  to  $29.17 \pm 19.76$  ng/ml ( $P = 0.120$ ).

After 6 months of intervention, both groups showed improvement in LVEF that only was significant in the case group (Table 2). The extent of changes between the two groups was significantly different ( $P < 0.001$ ) (Figure 2). 52% of the participants in the case group versus 7% in the control group improved in NYHA functional class.

The mean serum albumin increased significantly in both groups (0.26 g/dl in the case group,  $P < 0.001$ ; and 0.120 g/dl in the control group,  $P = 0.010$ ). Serum PTH did not change significantly in both groups ( $P < 0.050$ ). We followed the participants until 2 years after the study with a recommendation for adequate calcium and vitamin D supplementation. There was no significant difference in mortality in two groups (3 in the case versus 2 in the control group,  $P = 0.500$ ).

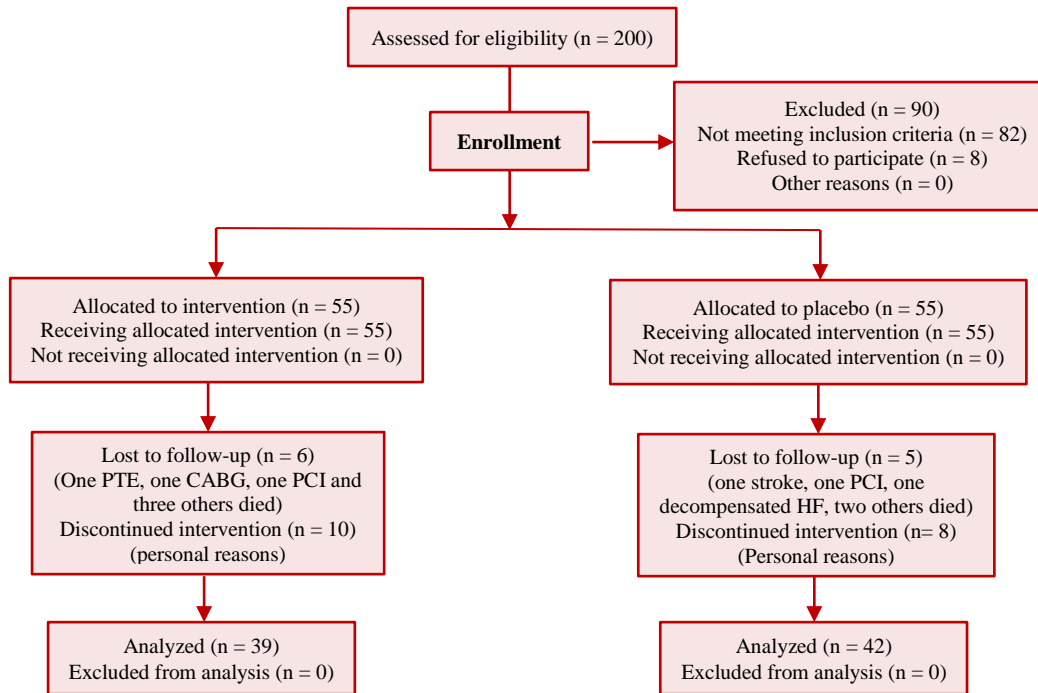
**Table 1.** Baseline characteristics of the participants

Characteristics	Study group (n = 39)	Placebo group (n = 42)	P*
Gender (men)	28 (71.8)	29 (69.0)	0.787
Cigarette smoking			0.554
Current	8 (20.5)	5 (11.9)	
Past	2 (5.1)	3 (7.1)	
CAD	26 (66.6)	20 (47.6)	0.120
HTN	23 (59.0)	31 (73.8)	0.160
Diabetes	10 (25.6)	12 (28.6)	0.767
NYHA			0.295
I	3 (7.7)	6 (14.3)	
II	27 (69.3)	29 (69.0)	
III	9 (23.0)	7 (16.7)	
Age (year)	$59.46 \pm 10.90$	$61.93 \pm 10.80$	0.316
LVEF (%)	$31.20 \pm 7.78$	$32.32 \pm 5.81$	0.436
LVESV (mm <sup>3</sup> )	$135.38 \pm 75.42$	$110.11 \pm 42.79$	0.070

Data are presented as mean  $\pm$  standard deviation (SD) or number and percentage

\*Independent t-test or chi-square test, as appropriate

CAD: Coronary artery disease; HTN: Hypertension; NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume



**Figure 1.** The study flow diagram based on Consolidated Standards of Reporting Trials (CONSORT) PTE: Pulmonary thromboembolism; CABG: Coronary artery bypass graft; PCI: Percutaneous Coronary Intervention; HF: Heart failure

### Discussion

Our study showed that weekly 50000 IU vitamin D supplementation for six months improved NYHA functional class and LVEF of patients with HF. This improvement was independent of supplementary calcium intake. We also observed a significant improvement in the left ventricular end-systolic volume (LVESV) that has been an independent predictor of survival in patients with low ejection fraction (EF).<sup>20</sup> Other studies have shown positive effects of vitamin D in HF.<sup>21,22</sup>

The possible mechanisms underlying the beneficial

effects of vitamin D on myocardial function and HF may be related to its role in regulation of inflammation,<sup>23,24</sup> inhibition of myocardial cell hypertrophy and fibrosis<sup>25</sup> and adverse remodeling,<sup>26</sup> regulation of rennin-angiotensin-aldosterone system (RAAS),<sup>27</sup> metabolic effects of vitamin D on the cardiac muscle by affecting calcium, phosphorus, or other components of muscle contraction,<sup>28</sup> improvement of secondary hyperparathyroidism, which has been shown as a contributing factor to cardiac muscle dysfunction,<sup>28,29</sup> and direct effects of vitamin D, independent of calcium, phosphorus, or parathyroid.<sup>30</sup>

**Table 2.** The studied variables and changes from the baseline

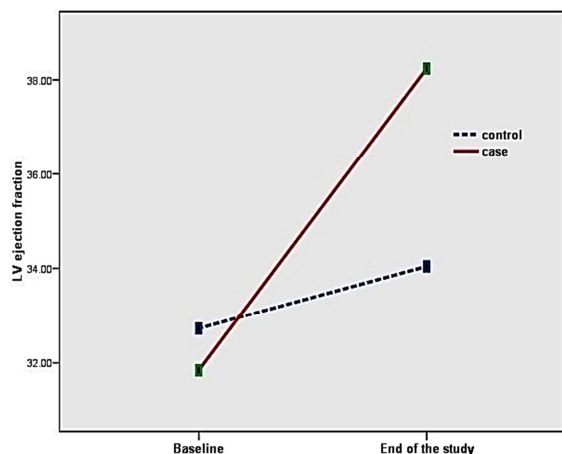
Variable	Baseline		P* (for baseline values)	Change from baseline		P* (for changes between groups)
	Case group	Control group		Case group	Control group	
25(OH)D (ng/ml)	25.85 ± 19.97	22.46 ± 22.28	0.940	33.91 ± 31.03**	6.21 ± 22.03	< 0.001
Calcium (mg/dl)	9.58 ± 0.54	9.43 ± 0.56	0.240	0.09 ± 0.74	0.24 ± 0.73	0.410
PTH (pg/ml)	33.03 ± 18.21	32.70 ± 22.22	0.960	0.83 ± 29.03	1.92 ± 22.93	0.870
Phosphate (mg/dl)	3.62 ± 0.58	3.65 ± 0.43	0.820	0.17 ± 0.61	0.14 ± 0.58	0.820
Creatinine (mg/dl)	1.11 ± 0.26	1.06 ± 0.29	0.510	-0.13 ± 0.17	-0.06 ± 0.19	0.130
Albumin (g/dl)	4.05 ± 0.28	4.03 ± 0.19	0.740	0.26 ± 0.37 <sup>‡</sup>	0.11 ± 0.23 <sup>‡</sup>	0.050
LVEF (%)	31.20 ± 7.78	32.32 ± 5.81	0.436	5.48 ± 4.46 <sup>‡</sup>	0.44 ± 5.62	< 0.001
LVES (mm <sup>3</sup> )	135.27 ± 72.75	109.90 ± 43.08	0.070	-27.92 ± 65.66 <sup>‡</sup>	-3.11 ± 17.54	0.020
NYHA functional class	2.15 ± 0.54	2.02 ± 0.56	0.300	-0.51 ± 0.51 <sup>‡</sup>	-0.05 ± 0.40	< 0.001

All values are shown as mean ± standard deviation (SD)

\*,\*\* Independent t-test or Mann-Whitney test, as appropriate; <sup>‡</sup> Change is significantly different from baseline within a subgroup (paired t-test)

PTH: Parathyroid hormone; LVEF: Left ventricular ejection fraction; LVES: Left ventricular end-systolic; NYHA: New York Heart Association





**Figure 2.** Left ventricular ejection fraction (LVEF) changes between groups from baseline to the end of the study

Inflammatory cytokine [tumor necrosis factor alpha (TNF- $\alpha$ )] decreases and anti-inflammatory cytokine [interleukin-10 (IL-10)] increases after 9 months of treatment by vitamin D in patients with HF in comparison to the control group.<sup>24</sup> Vitamin D<sub>3</sub> reduces the inflammatory milieu in patients with HF and might serve as a new anti-inflammatory agent for the treatment of the disease.<sup>23</sup> Active vitamin D (calcitriol) has anti-proliferating capability and might reduce myocardial hypertrophy and fibrosis.<sup>17,31</sup> Calcitriol has also a negative endocrine effect on the RAAS. Activated 1,25(OH)<sub>2</sub>D<sub>3</sub> suppresses renin gene transcription by blocking the activity of the cyclic adenosine monophosphate (cAMP) response element in the renin gene promoter<sup>32</sup> and inhibits renin secretion from the juxtaglomerular apparatus.<sup>27</sup> By reducing plasma rennin activity, it reduces angiotensin II levels and so, blood pressure.<sup>17</sup>

Most patients with HF in this study were in the stage of hypovitaminosis D ( $22.7 \pm 21.1$  ng/ml).<sup>10</sup> Other studies have also shown that patients with HF had mean serum concentrations around or below 20 ng/ml, i.e., in the insufficiency or even deficiency range.<sup>8-10,29</sup> The prevalence of low vitamin D status in cardiovascular disease (CVD) recently was reported 74% overall.<sup>33</sup>

Our results are consistent with other studies regarding the beneficial effects of vitamin D supplementation on exercise capacity, functional class, and left ventricular (LV) function in patients with HF.<sup>8,23,34</sup>

In some earlier animal and human studies, vitamin D deficiency rickets has been associated with HF<sup>28,35</sup> and its supplementation has improved

the condition.<sup>30</sup> Abdullah et al. introduced a five-month-old boy with severe dilated cardiomyopathy (DCM) with hypocalcemia due to vitamin D deficiency rickets. His cardiac function recovered completely after six months of vitamin D supplementation.<sup>36</sup> Amirlak et al. also reported two 9-month-old breastfed infants with congestive HF (CHF) secondary to DCM and advanced rickets. Following treatment with vitamin D and calcium supplements, both infants quickly recovered normal myocardial function.<sup>37</sup> Multiple similar reports of infants are present in the literature.<sup>38-40</sup> Alsafwah et al. reported that hypovitaminosis D was a contributory factor in decompensated HF in African Americans residing in Memphis, Tennessee, United States (US).<sup>41</sup> Pilz et al. also reported that low levels of 25(OH)D and 1,25(OH)<sub>2</sub>D were associated with prevalent myocardial dysfunction, deaths due to HF, and sudden cardiac death. They recommended interventional trials to elucidate the role of vitamin D supplementation for treatment or prevention of myocardial diseases.<sup>42</sup> Saadi et al. suggested that in Arab women, prevention and correction of vitamin D deficiency would reduce the incidence of HF and, with established HF and vitamin D deficiency, would improve cardiac function.<sup>19</sup> Recently, in a letter to the editor, Michi and Julies proposed that there might be some advantages in developing a dosage trial of vitamin D in the management of HF in pregnancy.<sup>43</sup>

We observed some improvement in LVEF in the control group. As the NYHA functional class of these patients did not differ from baseline, it may indicate that the improvement of LVEF in the control group does not have a clinical value.

At the end of the study, the biochemical parameters such as calcium, phosphorus, and PTH did not change significantly from the baseline. As patients with impairments of PTH-calcium axis were excluded from the study, and also participants of both groups received supplemental calcium, it seems that vitamin D benefits are unrelated to this axis and may confirm previous animal studies regarding its direct effects on the cardiac muscle.<sup>30</sup>

At the end of the study, serum albumin concentrations increased in both groups. This finding may be due to the close observation of these patients and improvement in health care of them during the study period and may be the effect of improvement on microalbuminuria in these patients.

Our study had some limitations. First, the small number of participants may limit recommending its use as a general recommendation. Second, the

duration of the study follow-up is not very prolonged, so judgment about survival benefits of vitamin D is not possible. The patients should be followed up for a more prolonged duration to assess the influence of this intervention on the survival rate.

### Conclusion

Treatment with vitamin D<sub>3</sub> improved LVEF and exercise capacity/NYHA functional class in patients with HF and might serve as a complementary agent for the future treatment of this disease.

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### Conflict of Interests

Authors have no conflict of interests.

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