

Original Article



An Empirical Study on the Effect of Short-Term Regular Vitamin D3 Supplement Therapy on Blood Pressure and Exercise Tolerance in Heart Failure Patients

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Trial Registration

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Conflict of Interest

The authors declare that they have no competing interests.

ABSTRACT

The receptor of vitamin D is expressed in almost all body cells, including vascular endothelial cells and cardiomyocytes. Vitamin D deficiency has been observed widespread amongst heart failure (HF) patients, which could have harmful effects on their health condition. This study aims to investigate the effect of vitamin D supplements on blood pressure (BP) and physical activity of HF patients. Thirty-nine systolic HF patients with low ejection fraction (EF) < 50% and class III of New York Heart Association functional classification were randomly divided into 2 groups including intervention and placebo to enroll in an 8 weeks double-blind clinical trial. During the trial 6-minute walk test (6MWT), 25-hydroxyvitamin D (25[OH]D) level, BP, sodium and potassium intakes were assessed. The mean 25(OH)D level increased to 28.9 ± 11.7 ng/mL ($p < 0.001$) in the intervention group. There was a poor but non-significant reduction in systolic BP (-0.033 ± 4.71 mmHg, $p = 0.531$) in the intervention group. The BP also did not change in the placebo group at the end of the trial. A negligible decrease of 6MWT was observed in the intervention group (-6.6 ± 29.2 m) compared to the placebo (-14.1 ± 40.5 m). However, differences between the 2 groups were not statistically significant ($p = 0.325$). The results solely showed a slight positive correlation between 25(OH)D level and 6MWT. No significant improvements in BP and 6MWT were observed after vitamin D3 supplementation.

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Keywords: Vitamin D; Heart failure; Blood pressure; Exercise test

INTRODUCTION

Heart failure (HF), in particular the type of discharged fraction that is referred to systolic HF, is a complicated and commonly progressive disease. It indicates the condition wherein the heart is unable to circulate blood well in normal infusion pressures, due to its structural or functional impairment. Its main symptoms are shortness of breath and fatigue, which ultimately leads to edema, and poor stamina; hence affecting the lifestyle of HF patients [1-4].

According to the study conducted in 2013, “It is estimated that almost 17 million people worldwide die annually from cardiovascular disease (CVD) of which at least 3-quarters belong to low- and middle-income countries” [5].

In Iran, the growth of mortality rates from CVDs is alarming [6]. According to past studies conducted on distinct ages, the vitamin D deficiency in Iran is highly prevalent [7-9].

The CVD, such as HF, is associated with numerous factors including smoking, alcohol consumption, physical inactivity, unhealthy diet, coronary artery disease, stroke, and high uncontrolled blood pressure (BP) [2,3,10,11].

Evidence suggests that lifestyle changes play prominent roles in preventing heart diseases and helping to manage them. Examples of lifestyle changes could be losing excess weight and engaging in regular moderate physical activity, along with a healthy and balanced diet [12,13]. Vitamin D3 is a lipid-soluble vitamin that is made up of 7-dehydrocholesterol produced in the skin over sunlight exposure [14]. Its receptor is expressed in all body cells, including vascular endothelial cells and cardiomyocytes [15]. The ubiquitous presence of the vitamin D receptors indicates the mediating effects of this vitamin on the other systems besides musculoskeletal tissue. This has led to extensive research on the function of vitamin D in the onset and progress of CVDs. Low concentrations of 25-hydroxyvitamin D (25[OH] D) in the serums of patients including high BP and HF have been observed [16]. Lower levels of this vitamin are associated with CVDs such as HF and hypertension [17]. Vitamin D could be beneficial for CVDs since it reduces inflammation and improves endothelial function by increasing the flow-mediated dilation through the renin-angiotensin system [18,19]. The recommended upper limit intake of vitamin D, according to Food and Nutrition Board of the Institute of Medicine, is 10,000 IU per day” [20].

Hence, taking vitamin D3 in moderate to high doses can reduce mortality in people with CVDs. This could be related to a decrease in the systolic and diastolic BP that has been reported in the heart disease patients with high BP [21,22].

The low levels of 25(OH)D in HF patients are associated with poor physical function. This could be measured by 6-minute walk test (6MWT), which has been defined as a beneficial prognostic test in HF diseases [23,24]. The correction of vitamin D deficiency is related with the improvement of 6MWT in these patients [25,26]. However, in some studies, vitamin D supplements failed to effect positively on physical function of the patients [27,28].

The wide variety dosages and duration have been used to correct the levels of vitamin D in HF patients with the aim of improving their health [19,29,30]. According to the Women's Health Initiative, low dosage of vitamin D (400 IU/day) had no considerable effect on CVDs [31]. Furthermore, in some studies, higher dosage (more than 100/000 IU/m) and also short-term supplementations had failed to effect significantly on HF patients' health condition [32,33]. In spite of such studies, there is still no significant evidence to answer the following question: “What is the optimal level of vitamin D that could have crucial role in the HF patients' health?” Therefore, we decided to examine the weekly administration of regular dosage of vitamin D to address the issue.

The importance of HF disease in the patients' quality of life and longevity from one hand, and the inconsistent results with no consensus on the effect of vitamin D in heart diseases

on the other hand justifies that further investigations are essential to ascertain the impact of vitamin D in heart diseases. Moreover, vitamin D deficiency is also associated with poorer muscle strength and physical performance [34]. Hence, improvement of vitamin D levels in HF patients may result in better physical performance and therefore affecting their quality of life. This research aimed to investigate the effect of vitamin D3 supplements on physical performance and BP in patients with stage III systolic HF and vitamin D deficiency.

MATERIALS AND METHODS

The general characteristics of the study population and study method were explained previously [35]. However, the assessment of BP and physical activity are the other points that have been considered here.

Participants, inclusion and exclusion criteria

This double-blind clinical trial study was conducted on systolic HF patients.

All of ischemic heart disease patients with New York Heart Association (NHYA) class III that were under HF treatment, including angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), diuretics, β blocker, calcium blocker, potassium blocker, aspirin, and nitroglycerin in the past 2 months were selected. All of the patients with $25(\text{OH})\text{D} \leq 20$ ng/mL and ejection fraction of less than 50% that measured by echocardiography were enrolled in the study.

Some individuals refused to continue the study and ultimately, 39 out of initial 44 patients remained in the study (**Figure 1**). The mean age of the participants was 63.00 ± 9.27 in the placebo group and 62.80 ± 11.86 in the intervention group as shown in **Table 1**.

From 39 patients who completed the study, 72.2% in placebo group and 66.7% in intervention group were male and the mean age of the placebo group and intervention group were 63.00 ± 9.27 and 62.80 ± 11.86 , respectively.

Table 1. Demographics and baseline characteristics of patients

Variables	Groups		p value
	Placebo (n = 18)	Intervention (n = 21)	
Mean age (yr)	63.0 \pm 9.2	62.8 \pm 11.8	0.955*
Mean baseline BMI (kg/m ²)	26.9 \pm 4.5	26.7 \pm 4.6	0.553 [†]
Sex			0.742 [‡]
Male	13 (72.2)	14 (66.7)	
Female	5 (27.8)	7 (33.3)	
Drugs			
ACE	14 (77.7)	12 (57.1)	0.182*
ARB	5 (27.7)	6 (28.5)	0.958*
Diuretics	3 (16.6)	4 (19.0)	0.852*
β -Blocker	9 (50.0)	10 (47.6)	0.886*
Calcium blocker	5 (27.7)	3 (14.2)	0.311*
Potassium blocker	2 (11.1)	2 (9.5)	0.875*
Aspirin	17 (94.4)	16 (76.9)	0.121*
Nitroglycerin	10 (55.5)	13 (61.9)	0.697*

Data are presented as number from total, percentage and mean \pm standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Independent t-test [†]Mann-Whitney test [‡] χ^2 test.

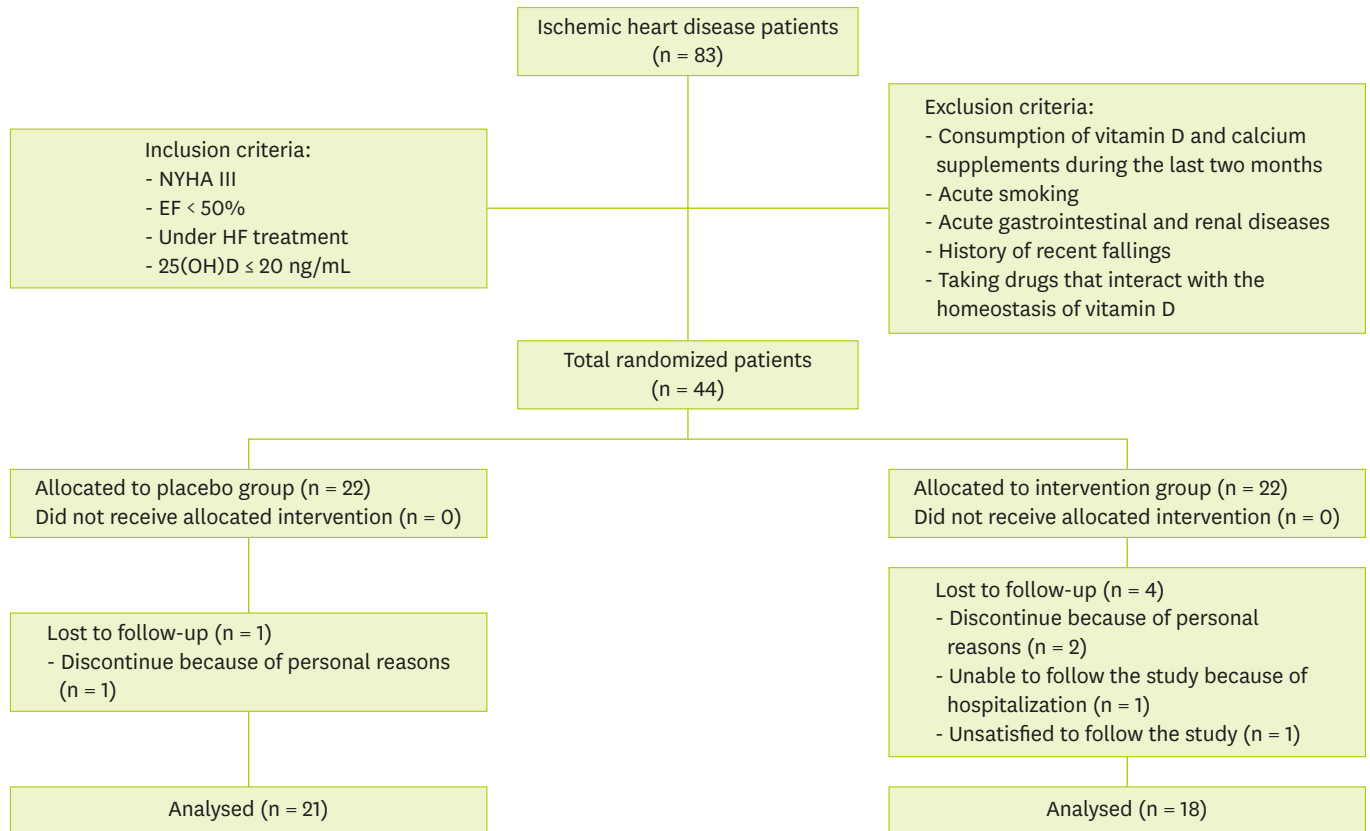


Figure 1. Flowchart of sampling method and randomization. NHYA, New York Heart Association; EF, ejection fraction; HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.

The following groups of patients were excluded from the study.

- Patients who were under the supplementation of vitamin D and calcium in the last 2 months;
- Patients with acute conditions in gastrointestinal diseases, smoking and renal diseases;
- Patients with the history of recent fallings;
- Patients who were taking prescriptions that could interact with the homeostasis of vitamin D including corticosteroids, antiepileptic drugs (AED), antibiotics, antifungals, cholestyramine and barbiturates during the last 6 months.

Study design and supplementation

Twenty-two patients were randomly selected to participate in each group. The patients at each group were listed based on block randomization scheme for unbiased assessment.

Participants received a single dose of vitamin D3 or placebo capsules per week for 8 weeks which were provided by Zahravi Pharmaceutical Company (Zahravi, Tehran, Iran). Both of the capsules had the same features in color, taste, shape, and size except for their contents (either 50,000 IU vitamin D3 or 100 mL oral paraffin). This dose was considered based on the guidelines for the correction of vitamin D deficiency in adults to attain a serum level of 25(OH)D above 30 ng/mL [36]. In addition, the Iran Ministry of Health has recommended the single and weekly dosage of 50,000 IU vitamin D3 up to 8 weeks to correct vitamin D deficiency among the Iranian population, which was exactly performed in our study.

It should be noted that all of the patients before the study were informed about the results of their serum 25(OH)D concentrations, and consciously participated in the study.

They were asked not to change their routine diet during the study period. The participants were instructed to report any missed dose or complications including symptoms of nausea, weakness, diarrhea, and any abnormal signs. Routine biweekly follow-up was set up with each participant over the phone to ensure that they were following the instruction.

Laboratory and clinical tests

The patients selected for this trial were all examined by cardiologist.

Blood samples were taken from the cephalic vein in a resting and sitting position before and after the intervention using a syringe. The samples were collected in early mornings, about 8 o'clock, before a meal was taken, by a trained phlebotomist for laboratory tests to measure the 25(OH)D level using an ELISA kit (Cat. No: 6411-9601; Euroimmun, Lübeck, Germany). We used 24-hour recall method for three days before and after supplementation for measuring the dietary intake of sodium and potassium. Then, their average intake was measured by modified Nutritionist IV version 4.1 software to assess Iranian foods (First Databank Division, The Hearst Corporation, San Bruno, CA, USA) [37].

BP was measured before and after supplementation by a trained nurse according to the standardized method and using a sphygmomanometer (ALPK, Tokyo, Japan).

Anthropometric measurements

The patients' weights were measured by a scale (Seca, Germany) in kilogram unit while dressing normally. The heights were measured in centimeter with a 0.1-cm accuracy, using a wall stadiometer. The measurements were performed by a trained person who was unaware of study objectives. The measured weight and heights were used to calculate the body mass index (BMI) of each patient before and after the supplementation period.

Physical function assessment

The 6MWT is an important prognostic parameter used to measure functional exercise endurance in chronic health failure patients. All subjects completed a standardized 6MWT before and after supplementation in accordance with American Thoracic Society (ATS) guidelines [38]. Subjects were asked to walk back and forth at a convenient speed, over a flat and unsupported pathway of 30 m for a period of 6 minute. Then walking distances were measured and recorded for analysis, and if any person failed to pass the test, after 15 minutes of resting, he/she repeated the test. The test was stopped by the cardiologist in the event of chest pain, any shortness of breath, signs of pallor and cramps in the leg.

Ethical approval

This study was performed on the guidelines stated by Declaration of Helsinki, and registered as IRCT2016102113678N13 in www.irct.ir site (The Iranian Registry of Clinical Trials). The reference code of the study by the Ethics Board of the Urmia University of Medical Science is IRUMSU.REC.1395. The written informed consent was obtained from all subjects and they could leave the study whenever they wanted.

Statistical analysis

In this study, SPSS software version 22 (IBM Corp., Armonk, NY, USA) was used for data analysis. Kolmogorov-Smirnov test was performed in order to verify the data normality. Wilcoxon signed ranks test and Mann-Whitney test were used to compare nonparametric variables within and between groups, respectively. Parametric variables were compared using independent t-test. Changes in the dependent variable and serum vitamin D were compared by partial correlation coefficient adjusted for sodium and potassium changes. For all tests, a significant level of 5% was considered.

RESULTS

There was a significance difference in the levels of 25(OH)D between two groups at the end of the study, as explained previously ($p < 0.001$; **Table 2**) [35]. No side effects of vitamin D intake were observed in the study.

No statistically significant difference between the groups regarding to HF and BP pharmacotherapy was observed (**Table 1**).

The mean of systolic blood pressure (SBP) decreased and there was an increase in the mean of diastolic blood pressure (DBP) in the intervention group, while both were increased in the other group. However, not all changes during the study in the 2 groups were statistically significant (**Table 2**).

There was not any significant difference in weight changes between the two groups before and after taking supplements ($p = 0.663$; **Table 2**). According to Wilcoxon test, both the placebo and intervention groups showed a significant decrease in sodium intake ($p = 0.007$ and $p = 0.002$, respectively). However, based on the covariance analysis model and the modulation of the effect of the sodium base values, no significant changes in the sodium levels were observed in 2 groups after intervention ($p = 0.615$). This was also the case for potassium level in placebo group confirmed by Wilcoxon test ($p = 0.349$). However, potassium levels decreased significantly in the vitamin D group ($p = 0.025$). After adjusting the effect of the received potassium base values, no significant difference was seen in its levels between the 2 groups ($p = 0.220$; **Table 3**).

The mean of 6MWT slightly decreased in the placebo group (from 229.0 ± 66.3 m to 220.6 ± 73.9 m; $p = 0.448$), whilst it did not change in the intervention group (228.5 ± 62.1 m to 229.2

Table 2. Effect of vitamin D3 supplementation on laboratory and clinical tests in HF Patients according to the groups of study

Variables	Groups								p value [†]
	Placebo (n=18)				Intervention (n=21)				
	Before	After	Change	p value*	Before	After	Change	p value*	
25(OH)D (ng/mL)	10.6 ± 5.1	12.9 ± 7.3	2.2 ± 5.1	0.071	10.5 ± 5.4	28.7 ± 11.7	18.1 ± 11.8	< 0.001	< 0.001
Weight (kg)	65.6 ± 6.0	65.7 ± 5.1	-0.0 ± 0.9	0.231	69.5 ± 17.2	69.5 ± 7.3	-0.0 ± -9.9	0.745	0.663
SBP (mmHg)	127.4 ± 12.9	127.8 ± 12.7	0.4 ± 1.1	0.114	124.7 ± 16.3	124.4 ± 12.6	-0.03 ± 4.7	0.531	0.318
DBP (mmHg)	80.4 ± 8.3	80.7 ± 7.9	0.3 ± 1.5	0.560	77.5 ± 10.7	77.6 ± 92.0	0.0 ± 3.9	0.943	0.907
6MWT (m)	229.0 ± 66.3	220.6 ± 73.9	-14.2 ± 40.5	0.448	228.5 ± 62.1	229.2 ± 69.5	-6.6 ± 29.2	0.365	0.325

Data expressed as mean ± standard deviation.

25(OH)D, 25-hydroxyvitamin D; SBP, systolic blood pressure; DBP, diastolic blood pressure; 6MWT, 6-minute walk test.

*Comparison between baseline and after intervention in both groups; †Comparison between 2 groups.

Table 3. Dietary intake of sodium and potassium according to the groups of study

Variables	Groups								p value [†]
	Placebo				Intervention				
	Baseline	Endline	Change	p value*	Baseline	Endline	Change	p value*	
Sodium consumption (mg)	3,762.6 ± 2,448.7	897.6 ± 247.9	-932.6 ± 1,199.2	0.007	2,200.0 ± 1,242.9	932.3 ± 314.3	-365.5 ± 670.5	0.002	0.615
Potassium consumption (mg)	2,577.3 ± 126.5	2,368.0 ± 567.5	-902.2 ± 1,506.3	0.349	2,611.5 ± 573.1	2,237.2 ± 552.3	-61.7 ± 1,049.8	0.025	0.220

Data expressed as mean ± standard deviation.

 *Comparison between baseline and after intervention in both groups; [†]Comparison between 2 groups.

Table 4. Partial correlation between changes in serum vitamin D levels and changes in other dependent variables

Variable	Correlation coefficient (r)	p values
25(OH)D	1.000	-
Weight change	0.107	0.539
SBP change	-0.194	0.272
DBP change	0.022	0.901
6MWT change	0.330	0.045

25(OH)D, 25-hydroxyvitamin D; SBP, systolic blood pressure; DBP, diastolic blood pressure; 6MWT, 6-minute walk test.

± 69.5 m; p = 0.365). Overall, there was no statistically significant change in 6MWT between 2 groups regarding the 6MWT variations (p = 0.325; **Table 2**).

Furthermore, the statistical analysis, using the correlation coefficient test, showed a moderate positive correlation between the 25(OH)D level and 6MWT (r = 0.33; p = 0.045; **Table 4**).

DISCUSSION

There were no significant changes in BP and 6MWT after the supplementation of vitamin D3. However, the 25(OH)D level increased significantly in the intervention group.

It is assumed that reducing BP can reduce stress on the vasculature, and may also lead to cardiovascular regeneration [39]. One of the suggested mechanisms that low levels of vitamin D can cause CVDs, including HF, is the increased activity of the Renin Angiotensin-Aldosterone System (RAAS) [40]. In contrast, some researches have mentioned that vitamin D supplementation can inhibit or down-regulate RAAS activity [41,42]. Pfeifer et al. [43] observed a significant reduction in SBP of senior women who received 1,200 mg calcium with 800 IU vitamin D3 daily. As mentioned above in this study, calcium supplements with vitamin D3 were used together. One possible explanation for the improvement of BP is to attribute the enhancement to the concurrent use of those 2 supplements. To avoid the overlap of calcium and vitamin D3 effects, we just considered vitamin D3 supplementation to assess the changes in the BP. In a review by Witham et al. [21], it has been asserted that there is a weak association between supplementation of vitamin D and BP in hypertensive patients. Our supplementation in HF also failed to alter the BP of the individuals.

One of the weakness for the current research is the reduction of the post-test sodium intake of both groups compared to the pre-test results, however, that was not significant between the 2 groups. One plausible explanation is that the BP did not improve during the study by vitamin D3 supplementation as sodium intake decreased. It is proved that sodium intake is one of the leading causes of rising BP with some potential impacts [44], which could be related to the function of kidney, hormones, nerves system, etc. [45]. In addition, it has

demonstrated that there is a strong relationship between having BP and HF [46]. Therefore reducing BP could be one of the important actions in managing and lowering CVD risks among patients [47].

Furthermore, according to the correlation coefficient test, a positive relationship between the 25(OH)D level and 6MWT was observed ($r = 0.33$). The correlation coefficient value indicates a moderate positive linear relationship. In other words, by one unit rise in the 25(OH)D level there is a 0.33 unit increase in 6MWT and ($p = 0.04$) that representing the weak relationship between the 2 variables.

Given the severity of HF and its progression to advanced NYHA classes, muscle strength indicators may decline. Relatively patients with chronic heart failure (CHF) with a higher NYHA class have less physical performance and more muscle weakness [48-50]. Similarly, low levels of 25(OH)D may also be in relation with muscle weakness [34], given that HF patients frequently have low serum concentration of vitamin D levels [51]. Therefore, it can be hypothesized that vitamin D supplementation can improve patients' physical performance, due to enhancing muscle strength. However, according to the findings of this trial, we did not reach to any positive significant changes in the 6MWT after eight weeks of supplementation. In a randomized double-blind trial by Witham et al. [27] with 100,000 IU vitamin D2 supplementation (2 doses, baseline and 10 weeks) in 105 patients with different heart conditions and heterogeneous problems, there was no change in 6MWT. Likewise, in a VINDICATE study by Witte et al. with one-year supplementation of 4,000 IU/day in 229 CHF patients, there was no change in the walking test; and long-term supplementation failed to increase the amount of 6MWT [33]. In another study conducted in 64 patients in 2 placebo and control groups with the supplementation of 50,000 IU/week vitamin D3 for 6 months, no improvement in HF patients' physical activity was shown at the end of the study [52]. These findings in previous studies are consistent with our results.

While in a study with 200,000 IU/week vitamin D3 supplementation for 12 weeks in 43 HF patients, the mean distance travelled by patients increased significantly from 806 ± 380 feet (about 245.6 ± 115.8 m) to 945 ± 393 feet (about 288.0 ± 119.78 m) ($p = 0.008$). Their study was a nonrandomized clinical trial and had no control or placebo group, and none of the patients was over 70 years of age [26]. Also, in another recent study by Amin et al. [25], 6MWT was significantly increased in 100 HF patients (both insufficient and deficient) that supplemented by 50,000 IU vitamin D3 per week for 8 weeks followed by supplementation of 50,000 IU every month for 2 consecutive months. The mean age of their study population was 45.25 ± 15.53 , and the study did not have a placebo or control group [25]. Considering that these studies did not have a control group with the same conditions, thus, no comparable results of the subjects were available. Also, the average age of the participants in these studies was lower compared to the current study. Therefore, it is reasonable to assume that the supplementation of young patients has better results in physical performance due to their higher muscular strength. Although there was no change in 6MWT in our study, the positive correlation depicts that this result may have been affected by long duration of the supplementation as it was observed in Majeed Babar et al.'s study [26].

The strengths of our study are as follows:

- The controlled experimental design with a placebo group;
- The use of regular-dose of vitamin D to determine its effect without calcium supplementation, which could make it difficult to draw conclusions about the vitamin D efficacy.

Nevertheless, this study has limitations that need to be addressed in future researches which include:

- The size of study sample was small, although it had sufficient statistical power;
- A short-term supplementation without maintenance therapy which, according to the guidelines [36], is required to achieving higher 25(OH)D levels.

CONCLUSION

According to the findings of the study the short-term vitamin D3 supplementation with vitamin D deficiency failed to improve BP and 6MWT in HF patients. However, a positive correlation between the 25(OH)D level and 6MWT has been observed. Thus improving 25(OH)D levels may possibly result in better physical performance in such patients. More vitamin D supplementation clinical trials in HF patients are needed to find any definitive relationship between vitamin D and BP and 6MWT.

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