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The Effect of Vitamin D Supplementation on Inflammation and Markers of Vascular Function in Heart Failure Patients

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Abstract

Objectives: Vitamin D deficiency is prevalent in heart failure (HF) and the anti-inflammatory impacts of vitamin D may affect the pathogenesis of HF. Therefore, the present study aimed to investigate the effect of vitamin D supplementation on echocardiographic and biochemical factors in vitamin D-deficient HF patients.

Materials and Methods: To this end, 39 HF patients with 25(OH)D ≤20 ng/mL participated in the current double-blind, randomized, and placebo-controlled trial, who belonged to class III, New York Heart Association classification. About 50 000 IU vitamin D3 (group D^+) or placebo (group D^-) were prescribed within 2 months. Then, the ejection fraction (EF%), tumor necrosis factor alpha (TNF-α), B-type natriuretic peptide (BNP), and high sensitive C-reactive protein (hs-CRP) were assessed before and after supplementation.

Results: The mean serum level of 25(OH)D increased markedly in D^+ group ($P<0.001$). The mean increase of EF% was 5.3±9.03% ($P=0.03$) and the decrease of TNF-α (-0.09 pg/mL, $P<0.001$) and BNP (-3.14 ng/mL, $P=0.04$) were statistically significant in D^+ group after supplementation. In addition, the blood concentration of BNP declined significantly in D^+ group compared to placebo while hs-CRP and TNF-α levels failed to differ between the two groups.

Conclusions: The results revealed that vitamin D could be effective against inflammation and thus its supplementation may reduce the severity of HF by improving the serum level of BNP and EF%. However, more clinical trials are required to approve the beneficial role of vitamin D in HF patients.

Keywords: Vitamin D, Heart failure, Tumor necrosis factor-alpha, Natriuretic peptide, Brain

Introduction

Heart failure (HF) is considered as a progressive chronic disease with the impaired cardiac ability to provide sufficient oxygen to the major body organs (1). The occurrence of HF is raising regarding the growing aging population and the optimism of HF patients toward life seems to be in line with better care and treatment of the patients (2,3).

According to Habibollahzade, "the Ministry of Health of Iran reported that the incidence of congestive HF was 3337 per 100 000 persons in 2001" (4). In a recent meta-analysis, the occurrence of vitamin D deficiency among the Iranian population was 45.64% and 61.90% in males and females, respectively (5).

In the medical literature, there are ample studies confirming the high risk of cardiovascular diseases (CVDs) among patients with vitamin D deficiency. Lately, renewed interests about the vitamin D role in non-skeletal conditions have focused on a wide range of chronic pathologies including skin and autoimmune diseases, cancer, diabetes mellitus, hypertension, and CVDs (6). However, epidemiological studies indicated inverse associations between vitamin D levels and CVD outcomes, especially in winter when there is limited access to sunlight (7). Therefore, to describe this inverse association, several pathophysiologic mechanisms were recommended (8) including the impact of vitamin D metabolites on blood pressure due to the renin-angiotensin system, the regulation of calcium levels, a reduction in the left ventricular mass, proinflammatory cytokines, and improvements in endothelial function (9-11).

B-type natriuretic peptide (BNP) level can serve as a prognostic marker in HF patients. BNP is a non-hormonal protein, that secrets through the cardiac ventricles after increasing the ventricular wall stretch, and can act as a survival predictor in HF patients compared to many traditional markers (12-14).

Genesis and the exacerbation of atherosclerosis by inflammation is confirmed and the results of former research (15) show that patients with CVDs have high blood concentration of proinflammatory mediators such as tumor necrosis factor alpha (TNF-α). In addition, the C-reactive protein (CRP) is a sensitive indicator of systemic low-grade inflammation synthesized in the liver (16). Based on the results of a meta-analysis study, a direct link is observed between the plasma level of CRP and

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the increased risk of heart diseases, strokes, and vascular mortality (17).

Further, according to some in-vitro studies, vitamin D in the form of 1,25-dihydroxy vitamin D3 or calcitriol may prevent the suppression of proinflammatory cytokines and alter the activity of immune cells (18-20).

Although a handful of research has examined the role of vitamin D in various disorders by focusing on the inflammatory cytokine and mediators, limited studies with inconsistent findings are available on the relationship between this vitamin and proinflammatory parameters in vitamin D deficient HF patients. CVDs such as HF highly contribute to the patients' quality of life and the occurrence of vitamin D deficiency is extremely high in the context of Iran. However, unclear results are found about the impact of vitamin D in HF patients by low 25(OH)D levels. Therefore, due to the importance of HF treatment in patients' life expectancy, the present study was designed to evaluate the impact of vitamin D3 (i.e., calcitriol or 1,25-dihydroxy vitamin D3) supplementation on echocardiographic parameters including EF% and biochemical parameters such as the blood concentration of BNP, TNF-α, and high sensitive (hs)-CRP in HF patients with vitamin D deficiency. In other words, the study sought to find whether correcting vitamin D levels could adjust the desired factors and thus improve HF.

Material and Methods

Participants

The current double-blind, randomized, and placebo-controlled trial was performed on 44 patients with HF recruited at the cardiac clinic in Taleghani hospital, Urmia, Iran, between October 2016 and February 2017.

Participants were eligible for inclusion only if they had received congestive HF treatment during the last two months in which their HF was caused by ischemic heart disease thus, was classified as New York Heart Association class III symptoms by vitamin D level ≤20 ng/mL and ejection fraction<50%. The exclusion criteria included HF due to other causes such as drug, infection and myocarditis, supplemented with calcium and vitamin D during the last two months, acute gastrointestinal disease, smoking, under investigation for recurrent falls, renal disease or therapy with corticosteroids, antiepileptic drugs, tetracycline, ketoconazole, cholestyramine, as well as phenobarbital and phenytoin in the past 6 months, which have interaction with vitamin D homeostasis.

Study Design

First, all participants were divided into 2 groups using a computer and assigning a random number to each one. In addition, all the participants and researchers were blind to the randomization. Further, the patients were assigned to intervention (D^+) and placebo (D^-) groups each containing 22 cases and a block randomization scheme was used for randomization. Patients in the D^+ group were given none jelly capsule of 50 000 IU/wk of vitamin D3 while D^- group received a placebo.

The vitamin D3 and placebo capsules were equal in terms of their size, shape, color, and ingredients except for the vitamin D3 or paraffin, which both of them were purchased from Zahravi Pharmaceutical Company (Zahravi, Iran) and the placebo capsules contained 100 mL oral paraffin. The patients were encouraged to preserve their regular diets and prevent taking vitamin D and calcium supplements during the study. As a result, at last 39 out of the initial 44 patients cooperated with the researchers up to the end of the study.

Laboratory and Clinical Tests

Body weight was measured at the beginning of the study and 2 months of follow-up clinic visit by a trained field worker. Patients were asked to take off their shoes to measure their heights and remove their excess clothes to measure their weights. The measurement error for the heights and weights was considered 1cm and 0.1 kg by using a calibrated digital scale and stadiometer, respectively (Seca703, Seca GmbH & Co KG, Hamburg, Germany). Furthermore, the height and weight of the patients were utilized to calculate their body mass index.

The cephalic vein of the patients was used to take 5 mL blood samples after a 12-hour overnight fast, the serum samples were frozen and kept at -80°C till the end of the study, and finally, centrifuged 20 minutes at room temperature and analyzed. All the biochemical parameters were estimated by a standard laboratory technique at baseline and two months after supplementation. The above-mentioned parameters measured using ELISA kits included BNP (Zell Bio GmbH, Germany Cat. No ZB-11287-H9648), high sensitive C-reactive protein (hs-CRP) (Zell Bio GmbH, Germany, Cat. No ZB-11805-H964), TNF alpha (Diaclone SAS, France, Cat. No: 950.090.096), and 25-hydroxyvitamin D (Euroimmun, Germany, Cat. No: 6411-9601).

Moreover, dietary consumption was measured using the 24-hour recall method for three days before and after supplementation for three days, which was accomplished by the trained nutritionists. Participants' daily intake of energy, micro- and macro-nutrients were estimated using the mean of three 24-hour dietary recalls. A modified Nutritionist IV software (version 4.1; First Databank Division, The Hearst Corporation, San Bruno, CA, USA) for the evaluation of Iranian foods was used to process nutrient consumptions. The ejection fraction% (by Samsung EKO 7 Ultrasound Machine) and New York Heart Association class were checked and determined by a cardiologist before and after supplementation.

Statistical Analysis

The obtained data were analyzed using SPSS software, version 22 (SPSS Inc, Chicago, IL). $P<0.05$ was considered significant in all statistical tests. In addition, the

Kolmogorov-Smirnov test was applied to evaluate the normal distribution of variables and non-parametric analysis was used if the distributions were not normal.

Further, the data were explained as mean and median and the percentages were utilized to represent categorical variables. Furthermore, the correlations of the serum level of vitamin D and dependent variables were performed using partial correlation test after adjusting for the covariates. Moreover, the Wilcoxon signed-rank test was employed to compare the variables before and after the treatment, followed by the Mann–Whitney U-test in order to investigate the differences between the D^+ and D^- groups.

Additionally, the Chi-square and Mann-Whitney tests were used to identify the covariates that may influence the primary outcome including smoking, a history of diabetes, and dietary consumption of micronutrients such as calcium and vitamin D. Eventually, the analysis of covariance was utilized by adjusting for the covariates in order to compare the changes from baseline between the study groups.

Results

Thirty-nine patients including 27 (~70%) men and 12 (~30%) women with a mean age of 62.89±10.61 years participated in this study. Twenty-one out of 22 patients and 18 out of 22 patients remained in the intervention and placebo groups, respectively (Figure 1). The demographic features of the patients are presented in (Table 1). Four patients withdrew consent to maintain in the study (Figure 1). As shown in Table 1, no significant difference is found between the groups of the study regarding baseline characteristics.

In addition, both D^+ and D^- groups demonstrate no significant difference respecting the dietary consumption of calcium and vitamin D at the first and end of the study (Tables 2 and 3).

However, the mean serum level of 25(OH) D indicates a marked increase from 10.55±5.44 ng/mL to 28.97±11.77 ng/mL in patients supplemented with vitamin D3 whereas, as expected, the placebo group shows a non-significant change. In other words, there is a statistically significant difference between the D^+ and D^- groups in this respect ($P<0.001$).

Table 3 presents the values of biochemical markers of the patients at baseline and after the treatment. As demonstrated, the improvement of ejection fraction% is statistically significant in D^+ group ($P=0.03$). Conversely, the blood concentration of tumor necrosis factor alpha (TNF-α) and BNP is significantly decreased in HF patients

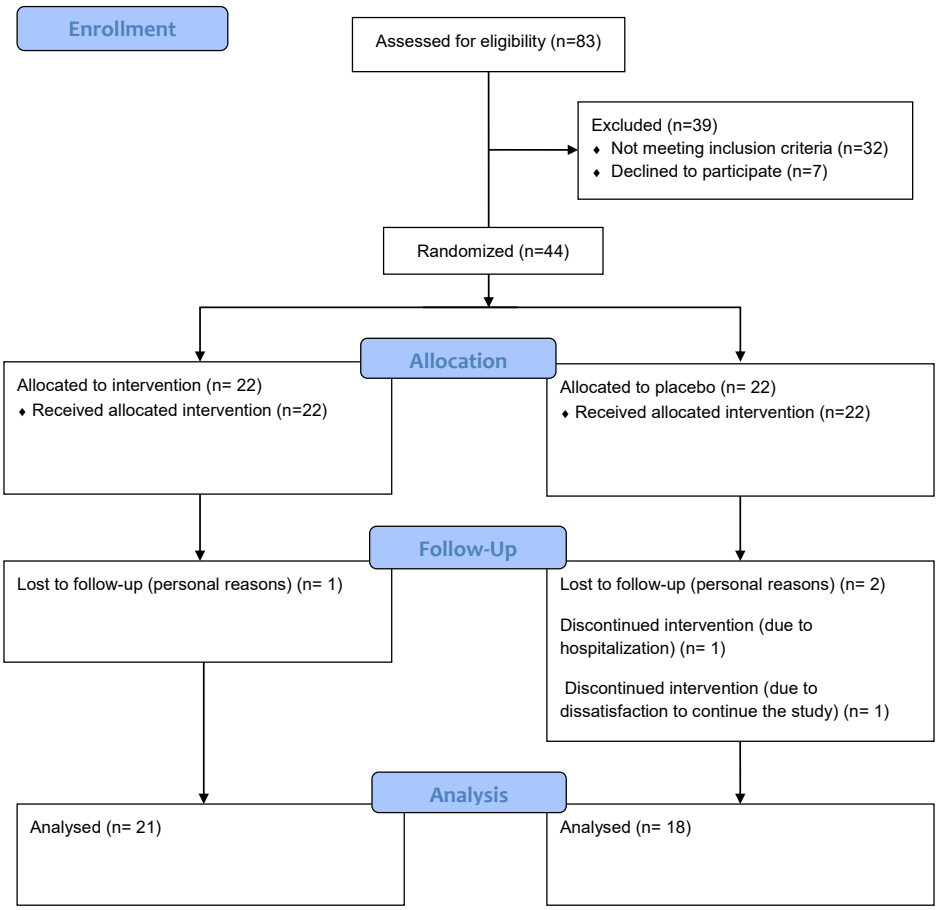

Figure 1. The Number of Included, Excluded, and Analyzed Patients.

Table 1. Patients' Baseline Characteristics According to Study Groups

Variables	Groups		*P* value
	D^- (n=18)	D^+ (n=21)	
Mean age (y)	63.00±9.27	62.80±11.86	0.967
Mean baseline BMI (kg/m²)	26.97±4.49	26.74±4.57	0.553
Smoking			
Yes	3 (16.7%)	6 (28.6%)	0.464
No	15 (83.3%)	15 (71.4%)	
Gender			
Male	13 (72.2%)	14 (66.7%)	0.742
Female	5 (27.8%)	7 (33.3%)	
Diabetes			
Yes	8 (44.4%)	7 (33.3%)	0.525
No	10 (55.6%)	14 (66.7%)	
25(OH)D (ng/mL)	10.69±5.12	10.55±5.44	0.934
ACE consumption	14 (77.77%)	12 (57.14%)	0.182
ARB consumption	5 (27.77%)	6 (28.57%)	0.958
Diuretics consumption	3 (16.66%)	4 (19.04%)	0.852
β-Blocker consumption	9 (50%)	10 (47.61%)	0.886
Ca blocker consumption	5 (27.77%)	3 (14.28%)	0.311
K blocker consumption	2 (11.11%)	2 (9.52%)	0.875
Aspirin consumption	17 (94.4%)	16 (76.9%)	0.121
Nitroglycerin consumption	10 (55.55%)	13 (61.90%)	0.697

Note. Data are expressed as Mean ± SD and the numbers as percentage; BMI: Body mass index; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; Ca: Calcium; k: Potassium; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

after treatment with D3 for 2 months (TNF-α: $P<0.001$; BNP: $P=0.04$) in comparison to the placebo group. Further, no significant change is observed in hsCRP level between the D^+ and D^- groups after supplementation ($P=0.099$), the details of which are provided in Table 3.

According to statistical analysis, there was no significant association between the changes in the level of 25(OH)D and BNP with other studied factors using the correlation coefficient test.

Table 4 represents the impact of vitamin D3 supplementation on NYHA classification change. Among the 18 patients in D^- group, 8.3%, 8.3%, and 93% are in New York Heart Association (NYHA) II, NYHA IV, and NYHA III classifications after vitamin D supplementation during the two months, respectively. All the patients were in NYHA class III at the baseline. The distribution of patients in the D^+ group in NYHA from I to IV classification are 6.3%, 18.8%, 75%, and 0% at the final stage of the study. Therefore, improvement is observed in the NYHA classification in the intervention group compared to the baseline ($P=0.05$). However, there are no statistical changes in the D^- group ($P=0.99$).

Discussion

Based on the results of this randomized clinical trial, the supplementation of HF patients with 50 000 IU vitamin D/wk was effective in achieving the normal range of serum vitamin D in 2 months.

Controversy remains regarding the appropriate level of vitamin D in the healthy population, especially about its non-calcemic effect (22). According to the World Health Organization, vitamin D deficiency of 25(OH)D level ≤20 ng/mL and serum 25(OH)D level of 20-30 ng/mL are considered as vitamin D insufficiency (23). Although, according to the Institute of Medicine and based upon the classic impact of vitamin D on bone health, vitamin D deficiency is described as 25(OH)D<20 ng/mL, the current guidelines have consistent recommendations for 25(OH)D levels more than 30 ng/mL.

Currently, there are few studies about the non-calcemic advantages of vitamin D in HF patients. Therefore, the appropriate level of vitamin D deficiency has not been specified in different conditions including HF patients, which can be different from the general population. However, other studies among patients with liver dysfunction used different definitions of vitamin D deficiency as 25(OH)D levels <10 ng/mL (24, 25). Accordingly, more investigations are demanded to determine the non-calcemic properties of vitamin D among HF patients. Furthermore, similar to the present study, Zia, by using a similar dose and period of vitamin D supplementation, confirmed the enhancement in ejection fraction% (EF%) from 24.3±1.7% to 31.3±4.3% in HF patients (26).

Table 2. Dietary Consumption of Calcium and Vitamin D According to Study Groups

Variables	Groups								*P* value**
	D^-				D^+				
	Before	After	Change	*P*-value*	Before	After	Change	*P* value*	
Dietary intake of Calcium (mg/d)	798.75±216.69	693.27±94.37	-105.46±217	0.102	743.64±183.54	706.76±169.66	-36.88±162.32	0.274	0.482
Dietary intake of Vitamin D (international units/day)	0.36±0.31	0.40±0.30	0.04±0.44	0.711	0.67±0.54	0.44±0.37	-.023±0.59	0.192	0.894

Data are expressed as mean ± SD.
* Comparison between before and after treatment in each group.
** Comparison between the two groups.

Table 3. The Effect of Vitamin D3 Supplementation on the Investigated Factors According to Study Groups

Variables	Groups								*P* Value**
	D-				D+				
	Before	After	Change	*P* Value*	Before	After	Change	*P* Value*	
25(OH)D (ng/mL)	10.69±5.1	12.94±7.3	2.25±5.08	0.071	10.55±5.44	28.67±11.7	18.12±11.77	<0.001	<0.001
BMI (kg/m^2)	26.97±4.49	26.26±4.80	-0.71±1.02	0563	26.74±4.57	26.70±4.75	-0.04±1.87	0.382	0.450
EF (%)	25.00 (25.00)	22.50 (25.00)	0.00 (15.00)	0.334	30.00 (25.00)	37.50 (35.00)	2.50 (30.00)	0.034	0.191±
TNF-α (pg/mL)	6.02 (6.41)	2.80 (2.002)	-4.12 (7.51)	0.116	4.31 (18.03)	2.60 (3.43)	-.091 (21.72)	<0.001	0.688±
hs-CRP (ng/mL)	6997.20 (6431.68)	7075.01 (8869.12)	179.93 (14046.15)	0.744	7073.53 (6822.62)	5698.67 (8077.03)	-817.35 (12723.70)	0.099	0.288±
BNP (ng/L)	2176 (1476.75)	1863.63 (1459.46)	2.47 (83.58)	0.149	1814.07 (1114.53)	1544.12 (1003.00)	-3.14 (278.21)	0.044	0.047±

Data are expressed as mean ± SD and median (range); BMI: Body mass index.
* Comparison between before and after treatment in each group.
** Comparison between the two groups.

Table 4. The Effect of Vitamin D3 Supplementation on NYHA Classification Change According to Study groups

Groups	Before	After				*P* Value*	*P* Value**
	NYHAIII	NYHAI	NYHAII	NYHAIII	NYHAIV		
Vitamin D3	100%	6.3%	18.8%	75%	0.00%	0.059	0.164
Placebo	100%	0.00%	8.3%	83%	8.3%	0.99	

Data are expressed as percentage; NYHAI: New York Heart Association.
* Comparison between baseline and after treatment in each group.
** Comparison between the two groups.

Left ventricular (LV) remodeling is a complicated process which refers to the alterations in ventricular architecture with the growth and death of cardiac myocyte, fibrosis, vascular rarefaction, inflammation, and electrophysiological remodeling (27). Pathologic LV remodeling with dilatation and impaired contractility is closely related to the reduction of EF% (28). Khalili et al performed a cross-section study among 139 patients with the occurrence of 72.7% of 25(OH)D deficiency and reported a significant inverse association between the serum level of 25(OH)D with MMP-9 as an early remodeling biomarker and with patients' mortality after an acute myocardial infarction (29). Furthermore, some previous studies suggested several mechanisms regarding the role of vitamin D in the proliferation of vascular smooth muscle cell, the calcification of the vessel inflammation, endothelial cell vasodilation, as well as the suppression of the renin-angiotensin system, insulin resistance, and blood pressure that can clarify the protective impacts of vitamin D on the occurrence of CVDs (30-32).

The results of the present study confirmed that the supplementation of calcitriol in vitamin D deficient HF patients markedly improved EF%. According to some studies, reducing the LV function results in a low EF associated with cardiac dysfunction and HF (33,34). As already mentioned, vitamin D supplementation can reduce BNP concentration in HF patients (35,36). Considering the relationship between LV dysfunction and high levels of BNP in HF (37), an improvement was expected in the EF% of the patients by improving vitamin D deficiency while decreasing the concentration of BNP. The results of the current study are in line with those of several previous studies conducted among HF patients which reported the beneficial role of vitamin D supplementation in the improvement of EF% (38,39).

The other noticeable result of the present study indicated that the blood concentration of proinflammatory cytokines including TNF-α just in the D+ group and BNP in the D+ group and between the groups reduced significantly after two months. Other studies suggested the contribution of the high levels of TNF-α in the pathogenesis and development of congestive HF (40) or that the TNF-α release may suppress by the change in the calcitriol dose (41).

Similarly, Amin et al (13) found a significant decrease in plasma level of BNP after four months supplementation of vitamin D3 among HF patients who had serum levels of 25(OH)D≤30 ng/mL at baseline. Regarding the association between vitamin D levels and cardiac cells function, previous studies demonstrated a relationship between lower vitamin D levels and the growth of cardiac cells and hypertrophy, which could motivate BNP secretion (42). Moreover, the release of BNP in acute HF was found to have an important effect on the acute increments of ventricular volume by several mechanisms including the vasoconstriction conflict, the retention of sodium, and the antidiuretic impacts of the activated renin-angiotensin-aldosterone system (RAAS) (43).

As previously mentioned, the suppressing effect of vitamin D on TNF-α was confirmed by previous experimental studies (44,45). Additionally, earlier research represented the regulatory impact of TNF-α concentration on the pathogenesis and exacerbation of chronic HF (46). Schroten et al (47) in their open-labeled study investigated the impact of daily 2000 IU vitamin D3 on pro-inflammatory cytokines in congestive HF patients for 9 months and showed a significant decrease in TNF-α whereas a significant increase in IL-10 levels. However, no changes were observed in BNP. Moreover, Shedeed reported a significant increase in IL-10 while a reduction in TNF-α and IL-6 in HF infant after 12 weeks of 1000 IU vitamin D3 supplementation compared to the control infants (39). In another randomized study by Dalbeni et al (38), 23 elderly patients with vitamin D deficiency (vitamin D≤30 ng/mL) were supplemented by 4000 IU/day of calcitriol or placebo for 6 months. However, no considerable improvement was found in the plasma concentration of BNP between the studied groups.

The dose-dependent suppressing impact of vitamin D on TNF-α was demonstrated by in vitro studies as well. Moreover, the 1-α-hydroxylase enzyme converting the 25(OH)D to 1,25(OH)2D3 was expressed in various tissues such as immune cells. It is worth mentioning that the enzyme activity and local expression rely on the circulating level of 25(OH)D (48-50) and calcitriol can act through the RAAS (51). According to the evidence, the RAAS can be activated by low levels of 25(OH)D and thus increase the level of TNF-α (52). No statistical evidence was observed concerning hs-CRP level with vitamin D supplementation, which is in conformity with the result of the study by Boxer et al (53) where no significant changes were reported about the serum levels of hs-CRP and BNP after supplementation with weekly 50 000 IU vitamin D3 in HF patients by 25(OH)D ≤37.5 ng/mL. There are inconsistencies among limited studies in HF patients regarding the therapeutic role of vitamin D on regulating proinflammatory cytokines. Furthermore, the inadequate number of studies in HF patients, variations in doses delivered to the subjects, the route of administration, the duration of supplementation by vitamin D, as well as the internal differences in the studied samples regarding the stage of the disease and drug usage harden to conclude about the beneficial role of vitamin D in HF patients. Therefore, large-scale clinical trials are warranted in this respect.

Despite the important results, the present study had some limitations. The serum level of 25(OH)D increased to 28.67±11.7 ng/mL after two months of supplementation in the intervention group that is lower than the appropriate level of 25(OH)D for improving the non-calcemic functions of vitamin D. Other limitations of this clinical trial were almost the small size of the sample, the short duration of the study (2 months), and the lack of gender matching groups.

Conclusions

In general, the results showed that vitamin D had an anti-inflammatory effect which was reflected by a decline in the level of TNF alpha. In addition, supplementation of vitamin D reduced the severity of HF that was confirmed by the decrease in the serum level of BNP and by an improvement in the ejection fraction%.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

In the current study was implemented based on the rules of the Helsinki Declaration and the Ethics Board of the Urmia University of Medical Science approved all the procedures (The reference ethical code: IRUMSU.REC.1395). Additionally, it was recorded in the Iranian Registry of Clinical Trials (identifier: IRCT2016102113678N13; https://www.irct.ir/trial/13465). The informed written consent was obtained from all the patients.

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