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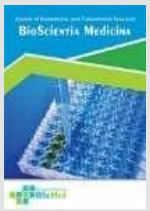

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The Effect of Giving Vitamin D Supplements on Improving Ejection Fraction in Heart Failure Patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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A B S T R A C T

Background: The role of vitamin D as an inflammation modulator, regulation system renin-angiotensin-aldosterone (RAAS), inhibits the production of parathyroid hormone (PTH), thereby causing left ventricular hypertrophy, causing hypocalcemia which induces hypertrophy in cardiac myocytes and can reduce cardiac contractility. This study aimed to determine the effect of giving vitamin D supplements on improving ejection fraction in heart failure patients at Dr. Mohammad Hoesin General Hospital (RSMH) Palembang, Indonesia. **Methods:** This study is an experimental study with a double-blind, randomized clinical trial design and uses primary data obtained from clinical examinations and supporting examinations of research subjects. A total of 40 research subjects participated in this study. **Results:** In this study, the median vitamin D level in the vitamin D supplementation group before treatment was 19.92 ng/dl (18.65-20.22), and in the placebo group was 19.74 ng/dl (18.14 - 20.13). After treatment with 1000 iu of vitamin D given for 3 months, the results showed that in the vitamin D supplementation group, there was an increase in vitamin D levels to 33.06 ng/dl (an increase of 13.14) with statistically significant results ($p < 0.05$). In the vitamin D supplementation group, there was an increase in ejection fraction to 37.9% (an increase of 3.65%) with statistically significant results ($p<0.05$). Contrasting results were shown in the group that received a placebo, where there was a decrease in ejection fraction to 33.15% (2.25% decrease). **Conclusion:** There is an improving effect of giving vitamin D supplements on increasing ejection fraction in heart failure patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

1. Introduction

Heart failure is still a major health problem in the world today. Heart failure is a complex clinical syndrome that is based on the heart's inability to pump blood to all body tissues adequately due to structural and functional disorders of the heart. One of the mechanisms causing heart failure is left ventricular myocardial dysfunction. Left ventricular myocardial dysfunction results in the left ventricle's ability to fill and pump blood. This dysfunction will cause a decrease in ventricular contractility and stiffness. This is described using left ventricular ejection fraction measurements. The ejection fraction is the end-diastolic volume minus the end-systolic volume divided by the end-diastolic volume. Cardiovascular disease accounts for 18.6 million deaths globally, and around 9.6% of deaths are caused by heart failure. Data from the American Heart

Association In 2020, an estimated 6.2 million adults had suffered from heart failure between 2013 and 2016. The prevalence of heart failure in the United States is predicted to increase by 46% from 2012 to 2030. In Indonesia, based on 2018 Basic Health Research data, the prevalence of congestive heart failure is 1.5% or around 1,017,290 people.[1-5]

Vitamin D has been known to play an important role in calcium absorption in the intestine. Since the past decade, the role of vitamin D has begun to be discovered in various non-skeletal conditions such as cancer/malignancy, high blood pressure, diabetes mellitus, cardiovascular disease, and infections. Vitamin D deficiency also makes heart failure worse. The influencing mechanism is the role of vitamin D as an inflammation modulator and regulation system renin-angiotensin-aldosterone (RAAS), which inhibits the production of parathyroid hormone (PTH), thereby causing left ventricular hypertrophy, causing hypocalcemia, which induces hypertrophy in cardiac myocytes and can reduce cardiac contractility.[6-10] This study aimed to determine the effect of giving vitamin D supplements on improving ejection fraction in heart failure patients at Dr. Mohammad Hoesin General Hospital (RSMH), Palembang, Indonesia.

2. Methods

This study is an experimental study with a double-blind, randomized clinical trial design and uses primary data obtained from clinical examinations and supporting examinations of research subjects. A total of 40 research subjects participated in this study, where the research subjects met the inclusion criteria. The inclusion criteria for this study were patients aged ≥ 18 years to 60 years who were diagnosed with heart failure based on history, physical examination, and echocardiography and were willing to take part in the research by signing an informed consent (informed consent) after explanation. Research subjects were grouped in a double-blind manner into treatment groups and control groups. The treatment group received vitamin D3 supplementation in soft capsules at a dose of 1000 IU per day for 12 weeks. Meanwhile, the control group received a placebo. This study has received approval from the medical and health research ethics committee of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

The parameter used to assess the ability of heart function is the percentage difference in blood volume in the diastolic and systolic phases relative to the blood volume in the diastolic phase. The ejection fraction value is divided into: HFrEF, where LVEF ≤ 40%, and HFmrEF where LVEF is 41% - 49%. Serum vitamin D levels are measured in accredited laboratories, where levels >30 ng/mL (75 nmol/L) are classified as normal, levels 20-30 ng/mL (50-75 nmol/L) are classified as vitamin D insufficiency and levels <20 ng/mL (<50 nmol/L) is classified as vitamin D deficiency. Data processing and analysis using the SPSS 25 program for Windows. Data is presented in the form of tables and graphs. Univariate data is divided into numerical and categorical data. If the data is numeric, use the normality test Sapphire Wilk and the homogeneity test Levene. The bivariate analysis will use tests Chi-square on categorical data and will use the T-test (if normally distributed) or Mann Whitney (if it is not normally distributed) on categorical and numerical data, then test the paired t-test (if normally distributed) or Test Wilcoxon (if distributed abnormally) to see the analysis before and after treatment.

3. Results

The majority of research subjects were male, both in the group that received vitamin D supplementation and those that received placebo, where statistically, there was no difference in gender between the group that received vitamin D supplementation and the group that received placebo, p> 0.05. In terms of age, it was found that the vitamin D supplementation group had an average age of 52.35 ± 6.13 and the placebo group 49.95 ± 7.07. All research subjects had an age range of 37-60 years, where statistically, there was no difference in age between the group that received vitamin D supplementation and the placebo group. The majority of research subjects had a high school education, both in the group that received vitamin D supplementation and those that received placebo, where statistically, there was no difference between the group that received vitamin D

supplementation and the group that received placebo, p> 0.05. The majority of research subjects had heart disease and hypertension, both in the group that received vitamin D supplementation and those that received a placebo, where statistically, there was no difference in CAD between the group that received vitamin D supplementation and the group that received placebo, but statistically, there was a difference in history of hypertension, between the group that received vitamin D supplementation and the group that received placebo. Based on BMI, it was found that the BMI in the vitamin D supplementation group was 23.97 ± 3.64, and in the placebo group, 24.09 ± 3.12. It can be concluded that both groups were classified as normal and obese, where statistically, there was no difference between the group that received vitamin D supplementation and the group that received placebo, p> 0.05.

Table 1. Characteristics of research subjects.

Research variable	Vitamin D supplementation group (n = 20)	Placebo group (n=20)	p*
Gender:			
Male	14	12	0,740
Female	6	8	
Age (years)	52,35 ± 6,13	49,95 ± 7,06	0,523
BMI (kg/m^2)	23,97 ± 3,64	24,09 ± 3,12	0,763
Education:			0,721
Primary school	3	3	
Junior high school	0	0	
Senior high school	12	14	
Bachelor/Diploma	5	3	
Previous illness			
CAD			
Yes	13	14	1,000
No	7	6	
Hypertension			
Yes	11	4	0,050
No	9	16	
DM			
Yes	4	3	1,000
No	16	17	

*Pearson Chi-Square, means if p < 0,05.

Table 2 presents the laboratory data characteristics of research subjects. Hemoglobin, leukocyte, platelet, instant blood sugar, urea, and creatinine levels did not show statistically significant differences in mean levels between the group that received vitamin D supplementation and the group that received placebo. The results of this study show that the characteristics of laboratory data between the group that received vitamin D supplementation and the group that received placebo were quite identical.

Table 2. Laboratory characteristics of research subjects.

Research variable	**Vitamin D supplementation group, Mean±SD**	**Placebo group, Mean±SD**	**p***
Hemoglobin (g/L)	12.68±1.94	13.12±1.25	0,400
Leukocytes (cells/mm^3)	8809±2543.53	9305±2816.53	0,562
Platelets (/uL)	310700±110836.58	264700±63029.73	0,115
Current blood sugar (mg/dL)	103.10±13.39	123.70±57.79	0,327
Urea (mg/dL)	45.75±24.99	51.81±67.49	0,314
Creatinine (mg/dL)	1.04±0.17	1.04±0.23	0,718

*Mann-Whitney test, significant if p < 0.05.

In this study, the median vitamin D level in the vitamin D supplementation group before treatment was 19.92 ng/dl (18.65-20.22), and in the placebo group was 19.74 ng/dl (18.14 - 20.13). After treatment with 1000 iu of vitamin D given for 3 months, the

results showed that in the vitamin D supplementation group there was an increase in vitamin D levels to 33.06 ng/dl (an increase of 13.14) with statistically significant results (p < 0 .05). Different results were shown in the group that received placebo where there was an increase in vitamin D levels to 19.95 iu (an increase of 0.21) where there was no statistically significant difference and was not statistically significant (p>0.05). The Mann-Whitney test was carried out to assess the difference in vitamin D levels after treatment between the group that received vitamin D supplementation and those that received placebo, and the results showed that vitamin D levels in the group that received vitamin D supplementation were higher than those that received placebo and were statistically significant and significantly different. (p < 0.05).

Table 3. Vitamin D levels before and after treatment.

Research variable	**Vitamin D supplementation group**			**Placebo group**			**p****
	Pre	**Post**	**p***	**Pre**	**Post**	**p***	
Vitamin D	19,92 (18,65-20,22)	33,06 (31,54-34,45)	0.000	19,74 (18,14-20,13)	19,95 (18,76-20,12)	0.380	0.000

p*: Wilcoxon test, p**: Mann-Whitney test, mean if p <0,05.

In this study, the average ejection fraction in the vitamin D supplementation group before treatment was 34.25%, and in the placebo group was 35.4%. After treatment with 1000 iu of vitamin D given for 3 months, the results showed that in the vitamin D supplementation group, there was an increase in ejection fraction to 37.9% (an increase of 3.65%) with statistically significant results (p<0.05). Contrasting results were shown in the group that received a placebo, where there was a decrease in ejection fraction to 33.15% (2.25% decrease), where there was no statistically significant difference and were not statistically significant (p>0.05). The Mann-Whitney test was carried out to assess the difference in ejection fraction after treatment between the group that received vitamin D supplementation and those that received a placebo, and it was found that the ejection fraction results in the group that received vitamin D supplementation were higher than those that received placebo and were statistically significant and significantly different (p < 0.05).

Table 4. Ejection fraction values before and after treatment.

Research variable	**Vitamin D supplementation group**			**Placebo group**			**p****
	Pre	**Post**	**p***	**Pre**	**Post**	**p***	
Ejection fraction (%)	34.25 (20,6-46,6)	37,9 (24-48,4)	0.000	35,4 (17,2-45,1)	33,15 (17,2-44,6)	0.390	0.000

p*: Wilcoxon test, p**: Mann-Whitney test, mean if p <0,05.

In this study, the median calcium level in the vitamin D supplementation group before treatment was 8.4 mg/dl, and in the placebo group was 8.45 mg/dl. After treatment with 1000 iu of vitamin D given for 3 months, the results showed that in the vitamin D supplementation group, there was an increase in calcium levels to 8.85 mg/dl (an increase of 0.45) with statistically significant results (p<0, 05). Contrasting results were shown in the group that received a placebo, where there was a decrease in calcium levels to 8.25 mg/dl (a decrease of 0.2 g/dl), which was also statistically significant (p < 0.05). The Mann-Whitney test was carried out to assess changes in calcium levels after treatment between the group that received vitamin D supplementation and those that received a placebo, and it was found that the calcium levels in the group that received vitamin D supplementation were higher than those that received placebo and were statistically significant and significantly different (p < 0.05).

Table 5. Calcium level values before and after treatment.

Research variable	Vitamin D supplementation group			Placebo group			p**
	Pre	Post	p*	Pre	Post	p*	
Calcium level (mg/dl)	8.4 (7.8-9,3)	8,85 (8-9,2)	0.000	8,45 (7.8-9.6)	8.25 (7.8-9)	0.011	0.000

p*: Wilcoxon test, p**: Mann-Whitney test, mean if p <0,05.

4. Discussion

After treatment with 1000 IU of vitamin D given to the supplementation group and placebo to the placebo group for 3 months, the results showed that in the vitamin D supplementation group, there was an increase in the median vitamin D level to 33.06 ng/dl (an increase of 13.14) with significant results, which is statistically significant with Wilcoxon *test* (p < 0.05). Different results were shown in the group that received a placebo, where the median change in vitamin D levels was 19.95 iu (an increase of 0.21), where there was no statistically significant difference and was not statistically significant (p>0.05). Mann-Whitney test to assess the difference in vitamin D levels after treatment between the group that received vitamin D supplementation and those that received placebo, and it was found that the vitamin D levels in the group that received vitamin D supplementation were higher than those that received placebo and were statistically significant and significantly different (p < 0 .05). These results are similar to other studies where giving 1000 iu of vitamin D to patients for 3 months showed a significant increase in vitamin D status (p= 0.003). In this study, the average vitamin D before treatment was 19.78 ng/ml, increasing to 26 ng/ml. Another study using 1000 iu of vitamin D gave the conclusion that giving 1000 iu was meaningful and could be used to achieve and maintain a vitamin D concentration of 30 ng/ml or more without vitamin D intoxication. Another study compared the administration of 1000 iu vitamin D supplementation. and 2000 iu results were obtained, and the conclusion was that both doses if consumed every day, could help maintain adequate vitamin D levels during the winter. However, a daily dose of 2000 IU is successful in maintaining desired vitamin D levels for a longer period of time. Thus, both doses of 1000 IU and 2000 IU have been proven to be safe and equally effective.[11-15]

In this study, the median ejection fraction in the vitamin D supplementation group before treatment was 34.25% (20.6, 46.6), and in the placebo group was 35.4% (17.2, 45.1). The results were similar to the study of Sugiri, et al at Dr. Kariadi General Hospital in heart failure patients, where the median ejection fraction in the study was 35% (10-76%).[9] However, the results were different from the ejection fraction in previous research conducted by Bilal at Mohammad Hoesin General Hospital, which was 39.8% (26-64.9). This is because in this study the inclusion criteria were patients with an ejection fraction < 50. After treatment with vitamin D 1000 iu given for 3 months in the supplementation group and placebo in the placebo group, changes were found in both groups. Results Wilcoxon test Pre and post-test ejection fraction in the vitamin D supplementation group was obtained p-value 0.000 or p < 0.05 which means that there is a significant change in ejection fraction which is statistically significant where there is an increase in the median ejection fraction to 37.9% (mean increase of 3.65%). Meanwhile, the results of the Wilcoxon test in the placebo group obtained a p-value of 0.390 (p > 0.05), which means the changes that occur are not significant and are not statistically significant where the ejection fraction tends to decrease, namely 33.15% (2.25% decrease). After that is, the Mann-Witney test to compare the effect of changes in ejection fraction in the two groups after treatment, a p-value of 0.000 or p < 0.05 was obtained, which means the change in the supplementation group was statistically significant. Another study by administering vitamin D supplements at a dose of 4000 iu and placebo to 229 samples for 1 year resulted in a significant and statistically significant increase in ejection fraction, namely 6.07% (p < 0.0001). Another study on heart failure patients with an average age of 74 years with vitamin D levels < 30 ng/ml by giving vitamin D

supplements of 4000 iu/day and placebo for 6 months concluded that giving vitamin D supplements could increase ejection fraction by 6. 71% (mean 40.5% to 47.2%) significantly and significantly (p: 0.042, p<0.05). Another study on 114 patients with chronic systolic heart failure by administering vitamin D supplements of 50,000 iu/week for 8 weeks resulted in an increase in ejection fraction of 5.46% (29.93±6.72% to 35.39±6.15%) overall. significant and statistically significant (p<0.001). In other studies, it was concluded that vitamin D supplementation could increase ejection fraction in patients with heart failure reduced ejection fraction compared to patients with reduced ejection fraction which is significant and statistically significant (p=0.03). This conclusion is also supported by other research on heart failure patients where it was found that there was a significant and statistically significant increase in ejection fraction with vitamin D supplementation (p= 0.006). This study used a vitamin D dose of 1000 iu which is different from several other studies which used higher doses and obtained the same significant results even though the increase in ejection fraction was lower than in external studies and did not reach the target. Research using vitamin D 1000 iu has been reported in other studies in babies with heart failure and found a significant and statistically significant increase in ejection fraction (p <0.01). Based on the AHA, it is said that heart failure with improved ejection fraction is when there is an increase in ejection fraction of more than 10% or increases to > 40% on follow-up measurements. Some of the mechanisms underlying the beneficial effects of vitamin D on heart function and heart failure are the role of vitamin D in inflammation, inhibiting hypertrophy and fibrosis and remodeling of heart cells, regulating the renin-angiotensin-aldosterone system, the metabolic effects of vitamin D on heart muscle by affecting calcium, phosphorus, or other components of muscle contraction, and the improvement of secondary hypoparathyroidism which have been known to have an influence on cardiac muscle dysfunction. Vitamin D3 reduces inflammation in patients with heart failure and may serve as a novel anti-inflammatory agent. Vitamin D has an antiproliferative ability and can reduce myocardial hypertrophy and fibrosis. Vitamin D is also known to have a negative effect on the renin-angiotensin aldosterone system by reducing renin activity in plasma, which will reduce angiotensin II levels so that it can lower blood pressure.[16-21]

In this study, the median calcium level in the vitamin D supplementation group before treatment was 8.4 mg/dl and in the placebo group was 8.45 mg/dl. After treatment with 1000 iu of vitamin D given for 3 months, the results showed that in the vitamin D supplementation group there was an increase in calcium levels to 8.85 mg/dl (an increase of 0.45) with statistically significant results (p<0, 05). Contrasting results were shown in the group that received placebo where there was a decrease in calcium levels to 8.25 mg/dl (a decrease of 0.2 g/dl) which was also statistically significant (p < 0.05). The Mann Whitney test was carried out to assess changes in calcium levels after treatment between the group that received vitamin D supplementation and those that received placebo and it was found that the calcium levels in the group that received vitamin D supplementation were higher than those that received placebo and were statistically significant and significantly different (p < 0.05). Another study showed that handling Ca^{2+} highly deformed, defined as a decrease in peak Ca^{2+} systolic and rate of transient decrease in Ca^{2+}, in rat cardiomyocytes via knockout 1α-hydroxylase (1α-OHase) [the key enzyme that catalyzes the production of $1,25(OH)_2D$], and treatment with paricalcitol, a vitamin D_3 analogue activated, significantly reduces Ca handling^{2+} on 1α-OHase$^{-/-}$ impaired cardiomyocytes. The main function of vitamin D is to optimize intestinal absorption of calcium and phosphorus so that proper formation of bone mineral matrix occurs. The active metabolite of vitamin D, namely 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), stimulates active calcium transport through the intestinal wall. This active metabolite binds to the vitamin D receptor in intestinal epithelial cells, then the calcium-binding protein CaBP-9K is synthesized, and the calcium channels TRPV6 and TRPV5 are activated. Calcium can enter cells from the intestinal lumen and is transported through the cells by calcium-binding proteins, then transferred to the

interstitium via the ATP mechanism. This active transport mechanism has a maximum limit. Apart from active transport, paracellular transport also occurs via diffusion. This paracellular transport depends on the calcium gradient, that is, on calcium intake. In the case of vitamin D deficiency, active transport is lower, and diffusion becomes more important, especially when calcium intake is high. Optimal vitamin D levels are necessary to increase the efficiency of calcium absorption. In other studies on patients with coronary artery disease, It was concluded that low calcium levels were independently associated with left ventricular systolic dysfunction in coronary artery disease ($p < 0.05$). In the heart, calcium has an important role in excitation–contraction coupling. The calcium trapped in the sarcoplasmic reticulum is not enough to initiate contractions; therefore, extracellular calcium influx is largely responsible for the initiation and magnitude of myocardial contractions. These findings support and provide a framework for understanding the pathophysiological relationship between extracellular hypocalcemia, especially low serum calcium concentrations, and cardiac dysfunction. Calcium balance in mitochondria is central to metabolic and mechanical regulation in cardiomyocytes. Calcium uptake into mitochondria alters ATP production and even controls apoptosis. In addition, mitochondria may directly establish transient changes in calcium within each beat and control local cytosolic [Ca] concentrations during the cardiac cycle. Calcium absorption is maintained due to the activity of mitochondrial Ca uniporter (MCU), mentioned the mitochondrial sodium/Ca exchanger (mNCX) affects calcium release. Interestingly, calcium uptake by mitochondria was found to strongly influence calcium signaling during contraction excitation processes and even partially influence transient changes in calcium. Another study showed that changes in mitochondrial calcium flux in rats with HFpEF were of greater amplitude and had changes in rise kinetics compared with lean and hypertensive animals. Decreased Ca levels in mitochondria leading to decreased ATP production and changes in reactive oxygen generation are considered to be the main characteristics of heart failure reduced ejection fraction (HFrEF).[21-26]

5. Conclusion

There is an improving effect of giving vitamin D supplements on increasing ejection fraction in heart failure patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

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