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Research Article

Vitamin D Deficiency can Accelerate Heart Failure: A Systematic Review and Meta-analysis

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Abstract

Background: Cardiovascular diseases (CVDs) are one of the most important causes of mortality all around the world. Studies have been shown that vitamin D is closely related CVDs, including heart failure (HF). We aim to assess the serum vitamin D levels in patients with HF in this meta-analysis.

Methods: A systematic research was performed in Pubmed, Web of Science, and Scopus databases for following keywords; "vitamin D level" OR "vitamin D status" AND "heart failure" until September 2020. Each step of the meta-analysis is appropriate to the PRISMA guideline. Totally, 2968 publications were screened and 16 articles were found to have suitable data. Analysis was done with RevMan 5.3. software. We also used GraphPad Prism 6 software for the correlation analysis and figures.

Results: Our pooled data showed that patients with HF had significantly lower levels of serum vitamin D compared to controls (REM $p < 0.00001$ mean difference: -8.20 [-10.46, -5.95]). There was also significant correlation between serum vitamin D level and left ventricular ejection fraction (LVEF) (p: 0.0134, r: 0.4785) (n = 26).

Conclusion: In this meta-analysis, it has been indicated that HF patients have lower serum vitamin D levels compared to controls. As seen in our study, vitamin D might be an important risk factor for HF, and vitamin D deficiency (VDD) may lead increased mortality caused by HF. Further researches are needed to elucidate which mechanisms play a role in the association between HF and vitamin D.

Keywords: Vitamin D; Vitamin D Deficiency; Cardiovascular Diseases; Heart Failure; Meta-analysis

Introduction

Vitamin D is a fat-soluble vitamin as well as being a steroid hormone, and it has two important forms, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [1,2]. Vitamin D is mainly produced in the skin via ultraviolet (UV) irradiation, and the rest is provided by diet [1]. Ergocalciferol is obtained by absorption of ergosterol in the duedonum, whereas cholecalsiferol is synthesized in the skin through UV irradiation of cholestrol precursor 7-dehydrocholestrol. Cholecalciferol and ergocalciferol are biologically inactive and they need further enzymatic conversions to form their active form. First, both of them are hydroxylated in the liver by 25-hydroxylase to become 25-hydroxyvitamin D (25(OH)D). Then, 25(OH)D is converted to calcitriol ($1,25(OH)D_2$), which is bioactive form of the vitamin, in the kidney by 1α-hydroxylase [2,3].

Vitamin D deficiency (VDD) is a general problem of the people around the world [1,2]. Several studies showed that VDD is associated with cardiovascular diseases (CVDs). The Framingham Offspring Study of 1739 patients showed that VDD is important risk factor for CVD [4]. The Cardiovascular Health Study of 2312 parti-

cipants who had not any CVDs at baseline demonstrated that lower levels of vitamin D are closely related with cardiovascular events [5].

Heart failure is a complex clinical syndrome that caused by a functional or structural cardiac abnormality [6]. It is one of the most important reason of mortality and morbidity worldwide and it is increasing in incidence and prevalence [1-3]. In recent years, several studies demonstrated an association between VDD and HF. The Intermountain Healthcare system study of 41,504 patients found that there is an significant association between serum vitamin D level and the incidence and prevalence of HF [7]. Similar data, which were obtained from epidemiological studies, showed that VDD is extremely prevalent in patients with HF [8,9]. Aparicio-Ugarriza., *et al*. and Cubbon., *et al*. indicated that VDD is an important risk factor for hospitalization and mortality in HF patients, respectively [10,11].

As a result, in the light of this information, we aimed to assess the serum vitamin D level in patients with HF in this meta-analysis. This meta-analysis is also important being the first meta-analysis that examining the association between serum levels of vitamin D and HF.

Methods

Eligibility criteria

Studies given serum vitamin D level in patients with HF data were screened. The mean and standard deviation were used for the meta-analysis of the data. The research was done with no limitation imposed on age, gender, race. The inclusion criteria were determined as; studies were giving the serum vitamin D level in patients with HF data in the form of mean and the standard deviation, using international units for biochemical parameters, giving the number of individuals.

Sources and search

Each step of the systematical search and data analyses were done according to the PRISMA guideline. Data were collected from PubMed, Web of Science, and Scopus databases without any restrictions on publishing date of the articles. Keywords were used as "vitamin D level" OR "vitamin D status," AND "heart failure" for all databases and data were collected until September 2020.

Statistical analysis

The I^2 was used for measuring heterogeneity (I^2% values of 0-25, 25-50, 50-75, and 75-100 represent no, low, moderate, and high heterogeneity) [12]. The fixed and random effect model was used according to the heterogeneity tau^2 value to give the results [13]. Cumulative meta-analysis was done with RevMan version 5.3 (Cochrane Collaboration, Copenhagen, 2014). GraphPad Prism 6 software was used for the correlation analysis and figures.

Bias analysis

Bias assessments were determined as described in the Cochrane guideline. Selection bias, performance bias, detection bias, attrition bias, and reporting bias were evaluated as low, unclear, or high risk according the information given in the studies [14].

Results

Cumulative meta-analysis

PubMed, Scopus, and Web of Science databases were systematically searched and 2968 publications were screened considering title, abstract and/or full text. 1091 publications were review/book chapters/conference papers or case reports/comment/editorial etc. Among 1877 publications 16 articles met with the inclusion criteria mentioned in figure 1 [15-30].

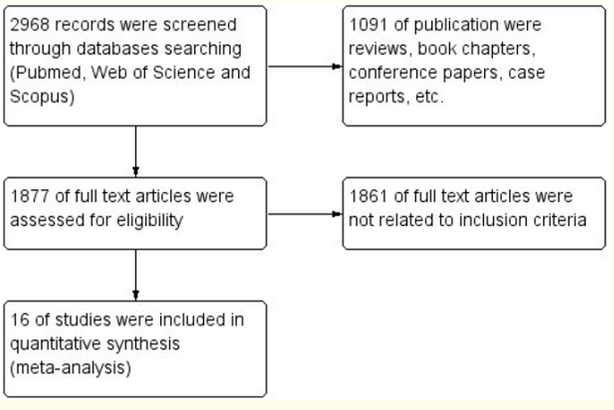

Figure 1: Included and excluded studies: Flow diagram.

Table 1 sums up the characteristics of studies. The 16 analyzed studies include 1187 patients and 667 controls. Among the 16 studies, eleven of them included healthy people as control group, four of them included patients who have not history of HF as control group, and one of them included hypertensive people as control group. Serum levels of vitamin D were cumulatively meta-analyzed in HF patients and their controls. Heterogeneity I^2 level was high (88%). Data showed that serum levels of vitamin D were significantly lower in patients with HF than controls (REM $p < 0.00001$ mean difference: -8.20 [-10.46, -5.95]) (Figure 2).

Study (Author – Year)	Study Type	Diagnosis	Case serum 25(OH)D (mean ± sd)	Case (n)	Control serum 25(OH)D (mean ± sd)	Control (n)	Determination of serum 25(OH)D level
Arslan 2019 [15]		Heart Failure	15.1 ± 10.2	157	29.1 ± 20.4	155	Radioimmunoassay
Atamañuk 2019 [16]	Cross-sectional study	Left Ventricular Failure	25.68 ± 12	42	28.8 ± 12	31	Electrochemoluminescence
Bozic 2010 [17]		Chronic Heart Failure	12.72 ± 5.96	73	19.68 ± 8.6	20	Chemiluminiscent immunoassay
Buleu 2019 [18]	Case-control study	Chronic Heart Failure and Coronary Artery Disease	20.49 ± 7.31	60	37.09 ± 4.59	60	Enzyme-linked immunosorbent assay
Cetin 2014-1 [19]	Observational study	Chronic Heart Failure and Non-ischemic Dilated Cardiomyopathy	14.3 ± 6.2	36	33.6 ± 14.3	25	Enzyme-linked immunosorbent assay
Cetin 2014-2 [19]	Observational study	Chronic Heart Failure and Ischemic Dilated Cardiomyopathy	15.8 ± 6.5	35	33.6 ± 14.3	25	Enzyme-linked immunosorbent assay
DiCarlo 2012 [20]	Pilot study	Heart Failure	20.4 ± 10.2	14	25.7 ± 11.1	14	Chemilluminescence immunoassay
Hamdy 2011 [21]		Congestive Heart Failure	36.4 ± 1	50	45.6 ± 1	20	Enzyme immunoassay
Kenny 2006 [22]		Heart Failure	26.6 ± 12.6	59	32.4 ± 9.6	23	Enzyme immunoassay
Kolaszko 2018 [23]	Cross-sectional study	Heart Failure and Coronary Artery Disease	31.5 ± 8.94	50	29.7 ± 10.2	77	Enzyme-linked immunosorbent assay
Lewandowski 2016 [24]		Chronic Heart Failure	10.86 ± 9.75	36	20.35 ± 7.33	41	Electrochemiluminescence
Loncar 2011 [25]		Heart Failure	12.8 ± 6	73	19.6 ± 8.8	20	Chemiluminiscent immunoassay
Loncar 2013 [26]		Heart Failure	12.72 ± 5.96	73	19.68 ± 8.6	20	Chemiluminiscent immunoassay
Nedeljkovic 2019 [27]	Prospective cohort study	Chronic Heart Failure	12.76 ± 5.92	68	19.56 ± 8.8	19	

Saponaro 2018 [28]		Heart Failure	18.1 ± 9.5	247	23.3 ± 9.6	76	High-performance liquid chromatography
Terrovitis 2012 [29]		Chronic Heart Failure	21.2 ± 10.8	60	25.2 ± 10	13	Enzyme-linked immunosorbent assay
Wu 2012-1 [30]		Heart Failure (HF New York Heart Association Class II-III)	34 ± 29	20	29 ± 14	14	Chemiluminescence immunoassay
Wu 2012-2 [30]		Heart Failure (HF New York Heart Association Class III-IV)	21 ± 11	34	29 ± 14	14	Chemiluminescence immunoassay

Table 1: Characteristics of included studies.

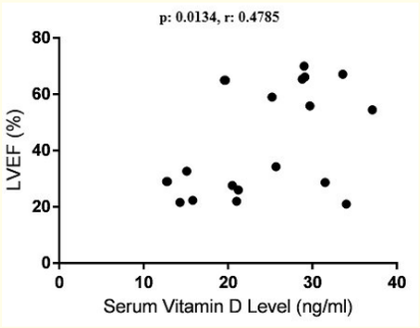

Figure 3: Graph of correlation between serum levels of 25(OH)D (ng/ml) and left ventricular ejection fraction (LVEF) (%).

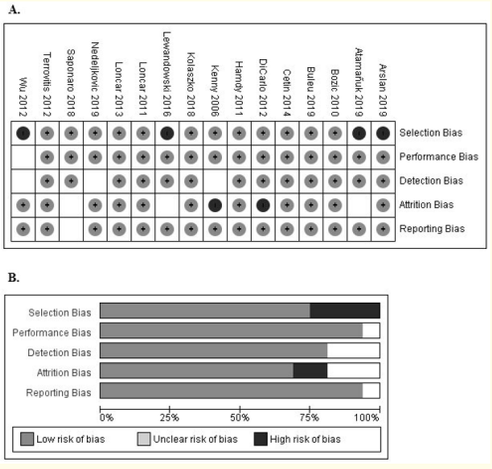

Figure 4: A. Risk of bias summary of the included studies for the meta-analysis. B. Risk of bias graph summary of the included studies for the meta-analysis.

Figure 2: A. Forest plots of serum levels of 25(OH)D in HF patients in comparison with controls. B. Funnel plots of of serum levels of 25(OH)D in HF patients in comparison with controls.

Correlation analysis

Serum levels of vitamin D were significantly associated with left ventricular ejection fraction (LVEF) (p: 0.0134, r: 0.4785) (n = 26) (Figure 3).

Risk of bias assessment

Bias analysis of each study were given with risk of bias summary and risk of bias graph (Figure 4).

Discussion

There are many biological situations that causes VDD such as age, obesity, malabsorption, inadequate sun exposure and kidney diseases and most recently, several studies demonstrated that VDD is associated with CVDs, including HF [1]. In this meta-analysis, we aimed to quantitatively determine the serum vitamin D levels in patients with HF compared to controls. At the end of the analyses, serum levels of vitamin D were found to be significantly lower in HF patients than controls.

There may be many possible biological mechanisms associated with VDD and HF. Vitamin D exerts its action through vitamin D receptor (VDR), which is expressed in many cells such as cardiomyocytes, and vascular and endothelial cells [3,31].

Endothelial dysfunction is an important problem for most of the CVDs, and it has been shown that vitamin D has many roles on endothelial cells through its receptor [31,32]. Martinesi., *et al*. indicated that $1,25(OH)_2D$ caused a significant reduction of adhesion molecule expression in endothelial cells [33]. In a study of Cardu´s., *et al*. found that calcitriol stimulates vascular smooth muscle cells (VSMCs) through the upregulation of vascular endothelial growth factor (VEGF) *in vitro* [34]. Also, calcitriol has been shown to increase production of endothelial nitric oxide, which plays an important role in CVDs [35].

Another important impact of vitamin D is about cardiomyocytes as mentioned before. Calcitriol is closely related with differentiation and growth of these cells [31,36]. In animal models, which were realized in VDR knockout (VDR KO) mice and rats, had been indicated that cardiac hypertrophy was observed as well as collagen accumulation [36-38]. Vitamin D may also play a role of extracellular matrix remodelling. In a study of VDR KO mice had been shown that unbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMs) caused a significant myocardial hypertrophy and fibrosis [2,36,39].

Vitamin D also has an important role of regulation of the renin-angiotensin-aldosterone system (RAAS) whose overproduction is associated with hypertension, cardiac enlargement, and sodium retention (32). Recent studies also demonstrated that lower levels of 25(OH)D and 1,25(OH)2D are closely related with upregulation of the RAAS [40-42].

In view of the roles of vitamin D in HF, many studies have been made to investigate the association between serum vitamin D level and HF, and the effects of vitamin D supplementation in HF patients. In a study, which is a prospective cohort of Italian adults, had indicated that VDD was closely related with increased risk for hospitalization in HF patients [43]. Similarly, Hou., *et al*. found that low serum vitamin D levels are serious problem for CVD mortality [44]. In a study by Pilz., *et al*. low levels of vitamin D have been shown as an important risk factor for mortality due to HF [45]. In a randomized controlled trial, it was shown that vitamin D supplementation did not improve quality of life (QOL) in HF patients [46]. Conversely, Moretti., *et al*. found that vitamin D supplementation made better QOL in HF patients [47].

There are certain limitations in our meta-analysis. One of them is that statistical heterogeneity is high. Nevertheless, statistical heterogeneity can be naturally observed in a meta-analysis and it should be considered when interpreting the data of this study. Another limitation is about serum vitamin D levels. There are several factors that affect vitamin D level in patients such as sun exposure or consuming foods, which are rich in vitamin D.

Conclusion

As a result, our meta-analysis demonstrated that HF patients have lower serum levels of vitamin D compared to controls. We want to say that more well-designed RCTs are needed to understand the biological mechanisms underlying this association and to examine the impact of vitamin D supplementation in this patients.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

Bibliography

1. D'Amore C., *et al*. "Vitamin D deficiency and clinical outcome in patients with chronic heart failure: A review". *Nutrition, Metabolism and Cardiovascular Diseases* 27.10 (2017): 837-849.

2. Brinkley DM., *et al*. "Vitamin D and Heart Failure". *Current Heart Failure Reports* 14.5 (2017): 410-420.

3. Meems LM vdHP., *et al*. "Vitamin D biology in heart failure: molecular mechanisms and systematic review". *Current Drug Targets* 12.1 (2011): 29-41.

4. Wang TJ PM., *et al*. "Vitamin D deficiency and risk of cardiovascular disease". *Circulation* 117.4 (2008): 503-511.

5. Kestenbaum B., *et al*. "Vitamin D, parathyroid hormone, and cardiovascular events among older adults". *Journal of the American College of Cardiology* 58.14 (2011): 1433-1441.

6. Yancy CW., *et al*. "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". *Journal of the American College of Cardiology* 128.16 (2013): e240-327.

7. Anderson JL., *et al*. "Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population". *American Journal of Cardiology* 106.7 (2010): 963-968.

8. Kim DH., *et al*. "Prevalence of Hypovitaminosis D in Cardiovascular Diseases (from the National Health and Nutrition Examination Survey 2001 to 2004)". *American Journal of Cardiology* 102.11 (2008): 1540-1544.

9. Gotsman I SA., *et al*. "Vitamin D deficiency is a predictor of reduced survival in patients with heart failure vitamin D supplementation improves outcome". *European Journal of Heart Failure* 14.4 (2012): 357-366.

10. Aparicio-Ugarriza R., *et al*. "Is vitamin D deficiency related to a higher risk of hospitalization and mortality in veterans with heart failure?" *Maturitas* 132 (2020): 30-34.

11. Cubbon RM., *et al*. "Vitamin D deficiency is an independent predictor of mortality in patients with chronic heart failure". *European Journal of Nutrition* 58.6 (2019): 2535-2543.

12. Higgins JPT., *et al*. "Measuring inconsistency in meta-analyses". *BMJ* 327.7414 (2003): 557-560.

13. Borenstein M., *et al*. "Fixed-effect versus random-effects models". *Introduction to Meta-analysis* 77 (2009): 85.

14. Higgins JP. "Cochrane handbook for systematic reviews of interventions version 5.1.0". *The Cochrane Collaboration* (2011).

15. Arslan AK and Tolunay H. "Analysis of Bone Mineral Density and Hip Fracture in Geriatric Patients with Heart Failure". *Konuralp Medical Journal* 11.2 (2019): 242-246.

16. Atamañuk AN., *et al*. "Vitamin D deficiency among patients with pulmonary hypertension". *BMC Pulmonary Medicine* 19.1 (2019): 258.

17. Bozic B., *et al*. "Relationship Between High Circulating Adiponectin With Bone Mineral Density and Bone Metabolism in Elderly Males With Chronic Heart Failure". *Journal of Cardiac Failure* 16.4 (2010): 301-307.

18. Buleu FN., *et al*. "Correlations between Vascular Stiffness Indicators, OPG, and 25-OH Vitamin D3 Status in Heart Failure Patients". *Medicina (Kaunas)* 55.6 (2019): 309.

19. Cetin M., *et al*. "Could decreased vitamin D levels be related with impaired cardiac autonomic functions in patients with chronic heart failure: an observational study". *Anadolu Kardiyol Dergs* 14.5 (2014): 434-441.

20. DiCarlo C., *et al*. "Body mass index and 25 hydroxyvitamin D status in patients with and without heart failure". *Congest Heart Fail* 18.3 (2012): 133-137.

21. Hamdy NM., *et al*. "Involvement of Depressive Catecholamines as Thrombosis Risk/Inflammatory Markers in Non-Smoker, Non-Obese Congestive Heart Failure, Linked to Increased Epidermal Growth Factor-Receptor (EGF-R) Production". *Indian Journal of Clinical Biochemistry* 26.2 (2011): 140-145.

22. Kenny AM., *et al*. "Femoral bone mineral density in patients with heart failure". *Osteoporosis International* 17.9 (2006): 1420-1427.

23. Kolaszko A., *et al*. "The Role of Parathyroid Hormone and Vitamin D Serum Concentrations in Patients with Cardiovascular Diseases". *Disease Markers* 2018 (2018): 5287573.

24. Lewandowski T BA., *et al*. "The evaluation of 25 (OH)D concentration in blood serum of chronic heart failure patients". *Current Issues in Pharmacy and Medical Sciences* 29.3 (2016): 107-110.

25. Loncar G., *et al*. "Association of increased parathyroid hormone with neuroendocrine activation and endothelial dysfunction in elderly men with heart failure". *Journal of Endocrinological Investigation* 34.3 (2011): e78-e85.

26. Loncar G., *et al*. "Association of adiponectin with peripheral muscle status in elderly patients with heart failure". *European Journal of Internal Medicine* 24.8 (2013): 818-823.

27. Nedeljkovic BB., *et al*. "Relationship of High Circulating Cystatin C to Biochemical Markers of Bone Turnover and Bone Mineral Density in Elderly Males with a Chronic Heart Failure". *Journal of Medical Biochemistry* 38.1 (2019): 53-62.

28. Saponaro F., *et al*. "Vitamin D measurement and effect on outcome in a cohort of patients with heart failure". *Endocrine Connect* 7.9 (2018): 957-964.

29. Terrovitis J., *et al*. "Bone mass loss in chronic heart failure is associated with secondary hyperparathyroidism and has prognostic significance". *European Journal of Heart Failure* 14.3 (2012): 326-332.

30. Wu C., *et al*. "Dynamics of bone turnover markers in patients with heart failure and following haemodynamic improvement through ventricular assist device implantation". *European Journal of Heart Failure* 14.12 (2012): 1356-1365.

31. Nitsa A., *et al*. "Vitamin D in Cardiovascular Disease". *In Vivo* 32.5 (2012): 977-981.

32. Beveridge LA and Witham MD. "Vitamin D and the cardiovascular system". *Osteoporosis International* 24.8 (2013): 2167-2180.

33. Martinesi M., *et al*. "1,25-Dihydroxyvitamin D3 inhibits tumor necrosis factor-α-induced adhesion molecule expression in endothelial cells". *Cell Biology International* 30.4 (2006): 365-375.

34. Cardús A., *et al*. "1,25-Dihydroxyvitamin D3 stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway". *Kidney International* 69.8 (2006): 1377-1384.

35. Molinari C., *et al*. "1α,25-Dihydroxycholecalciferol Induces Nitric Oxide Production in Cultured Endothelial Cells". *Cellular Physiology and Biochemistry* 27.6 (2011): 661-668.

36. Camici M., *et al*. "Vitamin D and heart". *Internal and Emergency Medicine* 8.1 (2013): 5-9.

37. Mancuso P., *et al*. "1,25-Dihydroxyvitamin-D3 treatment reduces cardiac hypertrophy and left ventricular diameter in spontaneously hypertensive heart failure-prone (cp/+) rats independent of changes in serum leptin". *Journal of Cardiovascular Pharmacology* 51.6 (2008): 559-564.

38. Simpson RU., *et al*. "Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse". *The Journal of Steroid Biochemistry and Molecular Biology* 103.3-5 (2007): 521-524.

39. Rahman A., *et al*. "Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice". *The Journal of Steroid Biochemistry and Molecular Biology* 103.3 (2007): 416-419.

40. Li YC., *et al*. "1,25-Dihydroxyvitamin D (3) is a negative endocrine regulator of the renin-angiotensin system". *Journal of Clinical Investigation* 110.2 (2002): 229-238.

41. Forman JP., *et al*. "Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans". *Hypertension* 55.5 (2010): 1283-1288.

42. Tomaschitz A., *et al*. "Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin–angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study". *Clinica Chimica Acta* 411.17 (2010): 1354-1360.

43. Costanzo S., *et al*. "Serum vitamin D deficiency and risk of hospitalization for heart failure: Prospective results from the Moli-sani study". *Nutrition, Metabolism and Cardiovascular Diseases* 28.3 (2018): 298-307.

44. Hou Y-M., *et al*. "Impact of serum 25-hydroxyvitamin D on cardiac prognosis in Chinese patients with heart failure". *British Journal of Nutrition* 122.2 (2019): 162-171.

45. Pilz S., *et al*. "Association of Vitamin D Deficiency with Heart Failure and Sudden Cardiac Death in a Large Cross-Sectional Study of Patients Referred for Coronary Angiography". *The Journal of Clinical Endocrinology and Metabolism* 93.10 (2008): 3927-3935.

46. Witham MD CL., *et al*. "The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial". *Circulation: Heart Failure* 3.2 (2010): 195-201.

47. Moretti HD., *et al*. "Vitamin D (3) repletion versus placebo as adjunctive treatment of heart failure patient quality of life and hormonal indices: a randomized, double-blind, placebo-controlled trial". *BMC Cardiovascular Disorder* 17.1 (2017): 274.

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