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Vitamin D supplements reduce depressive symptoms and cardiac events in heart failure patients with moderate to severe depressive symptoms

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Abstract

Background: Depressive symptoms and vitamin D deficiency predict cardiac events in heart failure patients, but whether vitamin D supplements are associated with depressive symptoms and cardiac events in heart failure patients remains unknown.
Purpose: The purpose of this study was to compare the association of vitamin D supplement use with depressive symptoms and cardiac events in heart failure patients with mild or moderate to severe depressive symptoms.
Methods: A total of 177 heart failure patients with depressive symptoms (Patient Health Questionnaire-9 score ≥5) completed a three-day food diary to determine dietary vitamin D deficiency. Patients were split into four groups by dietary vitamin D adequacy versus deficiency and vitamin D supplement use versus non-use. The Patient Health Questionnaire-9 was used to reassess depressive symptoms at six months. Data on cardiac events for up to one year and vitamin D supplement use were obtained from patient interview and medical record review. Hierarchical linear and Cox regressions were used for data analysis.
Results: Sixty-six patients (37.3%) had dietary vitamin D deficiency and 80 (45.2%) used vitamin D supplements. In patients with moderate to severe depressive symptoms, the group with dietary vitamin D deficiency and no supplements had the highest Patient Health Questionnaire-9 score at six months (β=0.542, p<0.001) and shortest cardiac event-free survival (p<0.001) among the four groups, the group with dietary vitamin D deficiency and no supplements didn't have the highest Patient Health Questionnaire-9 score at six months and shortest cardiac event-free survival in patients with mild depressive symptoms.
Conclusions: Vitamin D supplements predicted lower depressive symptoms and reduced cardiac events for patients with moderate to severe depressive symptoms. Vitamin D deficiency was associated with higher risk of shorter cardiac event-free survival in heart failure patients regardless of vitamin D supplementation.

Keywords

Heart failure, supplement, survival, vitamin D, depression

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Introduction

A low level of vitamin D has been commonly observed in patients with heart failure (HF).[1–3] More than half of patients with HF had inadequate intake of vitamin D compared to the recommended level of vitamin D intake for the general population.[4,5] Several prospective follow-up studies demonstrated that patients with low levels of serum vitamin D,[6,7] as well as inadequate intake of vitamin D,[8] were at a higher risk of hospitalization or death due to decompensated HF.

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The results of two meta-analyses suggested that approximately one in five HF patients had clinical depression, and patients with HF and depressive symptoms had a two-fold higher risk of secondary cardiac events than those with no depressive symptoms.[9,10] Lower levels of plasma vitamin D have been associated with a higher risk of incidence of clinical depression in patients with cardiovascular disease including HF.[11] In addition, the significant association between a lower level of serum vitamin D and depressive symptoms was found only in HF patients with insufficient level of vitamin D.[12] Furthermore, it was determined that depressive symptoms predicted a shorter cardiac event-free survival period only in HF patients with inadequate intake of vitamin D.[8]

In light of the link between depressive symptoms and low level of vitamin D, there have been clinical trials to reduce depressive symptoms with the use of vitamin D supplements in adults.[13,14] Meta-analyses have demonstrated that vitamin D supplementations were not effective to reduce depressive symptoms.[14,15] However, another meta-analysis showed that vitamin D supplementation was effective for patients with clinically significant depressive symptoms in sub-group analysis.[16] Based on the relationship between the high prevalence of depressive symptoms and low level of vitamin D in patients with HF, these patients may be ideal candidates for dietary intervention with use of vitamin D supplementation to reduce depressive symptoms and secondary cardiac events. However, no empirical data to support the hypothesis that vitamin D supplements reduce depressive symptoms and cardiac events in patients with HF who have different levels of depressive symptoms has been reported.

Therefore, the aim of this study was to determine the impact of vitamin D supplements on depressive symptoms and cardiac event-free survival in patients with HF and mild or moderate to severe depressive symptoms.

Methods

Design and setting

This study was a prospective, observational investigation of the impact of vitamin D supplements on depressive symptoms and cardiac events in HF patients with depressive symptoms. Patients were enrolled from outpatient HF clinics in a university-affiliated hospital in Seoul, Korea between April 2012–March 2014. Institutional review board approval for this study was obtained at the enrollment site. Before data collection, all patients who agreed to participate in this study signed written informed consent. This investigation conforms to the principles outlined in the Declaration of Helsinki.

Participants

The first author evaluated and confirmed the eligibility of cardiologist-referred patients to participate in this study. Patients were eligible for inclusion if they had the following: (a) a diagnosis of HF for longer than two years; (b) no change in prescribed renin-angiotensin system inhibitors or beta-blockers for at least three months prior to enrollment; (c) depressive symptoms determined using a Patient Health Questionnaire-9 (PHQ-9) score≥5;[17] and (d) the ability to read, write, and speak Korean.

Patients were excluded from this study if they had (a) an acute myocardial infarction, or any hospitalizations or emergency department (ED) visits within three months before enrollment, (b) a history of terminal illness such as cancer, severe thyroid disease, renal failure, or liver dysfunction, and (c) any obvious cognitive impairment defined as having a secondary diagnosis of cerebrovascular accident, dementia, or head trauma.

A total of 351 patients were eligible for this study. Eight patients declined to participate, six withdrew, 10 did not complete the food dairy or questionnaire, and four were lost to follow-up. One hundred and forty-six patients had a total PHQ-9 score<5. Thus, data from 177 patients were included in the final analysis.

Measurements and variables

Dietary vitamin D deficiency. Dietary intake of vitamin D was assessed with the use of a three-day food diary, which is known to be a reliable method to measure nutritional intake and dietary patterns.[18,19] At an outpatient HF clinic, the primary investigator provided a digital scale along with written instruction and explained to the patients how to measure and/or weight of food. The primary investigator also demonstrated how to use the food diary to record all foods eaten during the three-day period that included two weekdays and one weekend day. The next day after completion, patients brought their food diary to an outpatient HF clinic. More detailed information (e.g. ingredients, condiments, and brand names of processed foods) was obtained through a face-to-face interview between patients and the research assistant, who was blinded to patients' health status and clinical variables. The research assistant reviewed and analyzed their three-day food diary, and determined the average daily intake of vitamin D using the Computer-Aided Nutrition analysis program for professionals (CAN-Pro 4.0; APAC Intelligence, Seoul, South Korea).[20] Dietary vitamin D deficiency was defined as an average daily intake of less than 10 mcg of vitamin D for people under 65 years of age, and 15 mcg for those aged 65 and over, based on the recommended daily intake of vitamin D in the Dietary Reference Intakes for Koreans.[21]

Vitamin D supplementation. If patients answered 'yes' for the question, "Have you taken any dietary supplement for more than two weeks in the past year or more than once in the past month?,"[22,23] additional data about the types and doses of dietary supplements used were obtained. To

verify information regarding vitamin D supplementation, patients were asked to bring their supplements or provide a picture of label during the visit to the outpatient HF clinic. Based on this additional information of dietary supplements, whether dietary supplements included vitamin D or not was determined.

Depressive symptoms. Depressive symptoms were assessed at baseline and reassessed six months later using by the PHQ-9,[24,25] which consists of nine items related to depressive symptoms based on diagnostic criteria for major depressive disorders in the *Diagnostic and statistical manual of mental disorders*, 4th edition.[24,25] Each item is self-rated on a scale from zero (not at all) to three (nearly every day). The reliability of the Korean version of the PHQ-9 was previously reported with a Cronbach's alpha coefficient of 0.88.[17] In this study, the Cronbach's alpha coefficient for the nine items was 0.89. A total PHQ-9 score of 5–9 was categorized as mild depressive symptoms and 10–27 as moderate to severe depressive symptoms.

Other risk factors. The primary investigator collected data on other risk factors and these were confirmed by medical record reviews. Data included age, gender, living alone or living with other persons, body mass index, New York Heart Association functional class, etiology of HF, left ventricular ejection fraction, total comorbidity score calculated as the Charlson Comorbidity index,[26] and prescribed medications including anti-depressants.

Cardiac event-free survival. After baseline assessment, the research assistant made a phone call every month inquiring about all hospitalizations or ED visits during one year. If patients reported any event, the research assistant recorded the date and reasons for hospitalizations or ED visits on the hospitalization diary. Then, the primary investigator determined the date and main cause of events by review of electronic medical records. If a patient died during the one-year follow-up period, data about deaths were obtained from interviews with family members, hospital records, or death certificates. Cardiac event-free survival was defined as the time to first event of hospitalization, or death due to decompensated HF or cardiac problems during the one-year follow-up period. Therefore, the time and date for hospitalization were used in survival analyses for patients who were hospitalized due to decompensated HF prior to death.

Data analysis

Sample size. Considering a medium effect size of 0.15 and based on changes in depressive symptoms over 3–6 months, as reported in a prior study of depressive symptom trajectory,[27] α of 0.05, 80% power (1–β), and a total of up to 10 independent variables in multiple linear regressions, the minimum sample size of each group was determined to be 78 as estimated using the G*Power analysis software.[28]

Descriptive statistics. Descriptive statistics including means with standard deviations, medians with interquartile ranges, and numbers with frequencies were used to present the study variables. Comparisons between patients with mild and those with moderate to severe depressive symptoms were done using the chi-square or independent *t*-test.

Group comparisons. Patients were stratified into four groups according to dietary vitamin D adequacy or deficiency, and whether or not they were on vitamin D supplements as follows; (a) dietary vitamin D adequacy with vitamin D supplements, (b) dietary vitamin D adequacy without vitamin D supplements, (c) dietary vitamin D deficiency with vitamin D supplements, and (d) dietary vitamin D deficiency without vitamin D supplements. One-way analysis of variance with post-hoc test was used to compare the total PHQ-9 score re-measured at six months among those four groups.

Hierarchical linear regressions. The assumption of no multicolinearity was supported in this study with a tolerance value of 0.474–0.950, and a variance inflation factor of 1.082–1.609 (close to 1–2). Hierarchical linear regressions were conducted to determine the impact of vitamin D supplements on depressive symptoms after controlling for age, gender, living status, body mass index, New York Heart Association functional class, total comorbidity score, and use of anti-depressants. These risk factors were associated with depressive symptoms and health outcomes of patients with HF in previous studies.[27,29–33]

Hierarchical Cox proportional hazard regressions. The time-dependent covariate analysis was not statistically significant (p=0.643), indicating that the proportional hazard assumption was not violated. Hierarchical Cox proportional hazard regressions with the adjusted cardiac event-free survival curves were performed to determine the impact of vitamin D supplements on cardiac event-free survival after controlling for same risk factors. A hazard ratio with 95% confidence interval (CI) for cardiac events was determined for all independent variables. Data analysis was performed using SPSS for Window 23.0 (IBM, Armonk, New York, USA); p<0.05 was considered significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Almost one-third of the patients were females. Eighty-six patients

Table 1. Patient characteristics, *n*=177.

Characteristics		*n* (%) or mean (±SD)			*p* Value
		Total	Patients with mild depressive symptoms (*n*=95)	Patients with moderate to severe depressive symptoms (*n*=82)	
Age (years)		65 (±11)	65 (±12)	63 (±10)	0.241
Gender[a]	Male	119 (67.2)	72 (77.9)	45 (54.9)	0.001
	Female	58 (32.8)	21 (22.1)	37 (45.1)	
Living status	Living alone	54 (30.5)	30 (31.6)	24 (29.3)	0.437
	Living with someone	123 (69.5)	65 (68.4)	58 (70.7)	
Education level (years)		13.9 (±2.9)	14.2(±3.3)	13.6 (±2.7)	0.255
Body mass index (kg/m^2)		25.2 (±4.8)	25.3 (±5.1)	25.0 (±4.5)	0.659
NYHA class	I	21 (11.9)	11 (11.6)	10 (12.2)	0.466
	II	88 (49.7)	52 (54.7)	36 (43.9)	
	III	59 (33.3)	27 (28.4)	32 (39.0)	
	IV	9 (05.1)	5 (05.3)	4 (04.9)	
Left ventricular ejection fraction (%)		34.1 (±13.2)	34.1 (±13.2)	34.1 (±13.3)	0.987
Etiology of HF	Non-IHD	94 (53.1)	52 (54.7)	42 (51.2)	0.640
	IHD	83 (46.9)	43 (45.3)	40 (48.8)	
Total comorbidity score		3.0 (±1.8)	3.0 (±2.0)	3.0 (±1.7)	0.836
Medication	ACE inhibitors or ARB II	157 (88.7)	85 (89.5)	72 (87.8)	0.727
	Digoxin	37 (20.9)	22 (23.2)	15 (18.3)	0.427
	β blocker	116 (65.5)	65 (68.4)	51 (44.0)	0.385
	Diuretics	129 (72.9)	69 (72.6)	60 (73.2)	0.936
	Aldosterone antagonist	48 (27.1)	26 (27.3)	22 (26.8)	0.867
	Anti-depressant[a]	41 (23.2)	24 (25.3)	17 (20.7)	0.476
Dietary vitamin D intake (mcg/day)		13.2 (±6.7)	13.0 (±6.8)	13.5 (±6.6)	0.688
	Adequate	111 (62.7)	57 (60.0)	54 (65.9)	0.422
	Deficient	66 (37.3)	38 (40.0)	28 (34.1)	
Vitamin D supplements[a]					
	Yes	80 (45.2)	51 (53.7)	29 (35.4)	0.015
	No	97 (54.8)	44 (46.3)	53 (64.6)	

ACE: angiotensin-converting enzyme; ARBII: angiotensin II receptor blocker; HF: heart failure; IHD: ischemic heart disease; NYHA: New York Heart Association.

[a]$p<0.05$ in chi-square test or independent t-test.

(48.6%) were older than 65 years with a range of 32–89 years. Sixty-three patients (35.6%) had a normal weight with body mass index range of 18.5–22.9 kg/m^2. More than 60% of patients had heart failure with reduced ejection fraction defined as left ventricular ejection fraction of less than 40%. Approximately two-thirds of the patients had hypertension and 83 patients (46.9%) had diabetes. Forty-one patients (23.2%) were prescribed anti-depressants.

Depressive symptoms, vitamin D intake, and use of vitamin D supplements at baseline

The mean PHQ-9 score of the 177 patients with HF and depressive symptoms was 11.4±6.4. Ninety-five patients had mild depressive symptoms with a total PHQ-9 score between 5–9. Eighty-two patients had moderate to severe depressive symptoms with a total PHQ-9 score equal to or greater than 10.

The average intake of vitamin D was 13.2 mcg per day with a median value 12.0 mcg and a range of 3.1–30.9 mcg (interquartile range 7.2–16.4 mcg). Sixty-six patients (37.3%) had dietary vitamin D deficiency.

Eighty patients (45.2%) reported use of vitamin D supplements. Seventy patients reported use of multi-vitamin supplementations and 10 patients took only vitamin D supplements. Nineteen patients took multi-vitamin supplements, which did not include vitamin D. Daily intake by those taking vitamin D supplements ranged from 10–50 mcg. Thus, if a patient took a vitamin D supplement, their daily intake of vitamin D reached the recommended daily intake of vitamin D for healthy adults.

In bivariate analysis, women with HF had more severe depressive symptoms than men with HF (χ^2=10.583;

Table 2. Differences in depressive symptoms at six months among four groups stratified by dietary vitamin D deficiency and use of vitamin D supplements.

Groups		Patients with mild depressive symptoms (*n*=95)			Patients with moderate to severe depressive symptoms (*n*=82)		
		Total PHQ-9 score Mean (±SD)	*F*	*p*	Total PHQ-9 score Mean (±SD)	*F*	*p*
(a)	Vitamin D adequacy and vitamin D supplements	4.77 (±3.40)	5.563	0.001	2.45 (±3.30)	9.431	<0.001
(b)	Vitamin D adequacy and no vitamin D supplements	7.31 (±5.66)			6.64 (±4.43)		
(c)	Vitamin D deficiency and vitamin D supplements	5.86 (±5.28)			7.33 (±3.39)		
(d)	Vitamin D deficiency and no vitamin D supplements	10.13 (±5.94)			11.10 (±7.73)		
Total		6.78 (±5.29)			6.73 (±5.83)		

a<d[a], c<d[a] in patients with mild depressive symptoms; a<b[a], a<c[a], a<d[a], b<d[a] in patients with moderate to severe depressive symptoms.
[a]*p*<0.05 in Tukey HSD (honestly significance difference) post-hoc tests.

p=0.001). Among patients taking a vitamin D supplement, 51 (53.7%) had mild depressive symptoms and 29 (35.4%) had moderate to severe depressive symptoms, while 44 (46.3%) had mild depressive symptoms and 53 (64.6%) had moderate to severe depressive symptoms among patients who did not take a vitamin D supplement (χ^2=5.962; *p*=0.015) (Table 1).

The link of dietary vitamin D deficiency and vitamin D supplements to depressive symptoms at six months

At the six-month time point, 108 patients (61.0%) had depressive symptoms indicated by a PHQ-9 score ≥5. Table 2 shows the total PHQ-9 scores at six months among four groups stratified by dietary vitamin D deficiency and vitamin D supplements. In both groups with mild and moderate to severe depressive symptoms (*F*=5.563, *p*=0.001; *F*=9.431, *p*<0.001), patients with dietary vitamin D adequacy and vitamin D supplements had the least depressive symptoms, while those with dietary vitamin D deficiency and no vitamin D supplements had the most severe depressive symptoms (Table 2).

In patients with mild depressive symptoms (*n*=95), younger age (β=−0.262, *t*=−2.492, *p*=0.015) and use of anti-depressants (β=0.345, *t*=3.206, *p*=0.002) were associated with a higher level of depressive symptoms at six months; whereas dietary vitamin D deficiency and no supplements were associated with a higher level of depressive symptoms at six months in patients with moderate to severe depressive symptoms (*n*=82), controlling for age, gender, living status, body mass index, New York Heart Association functional class (β=0.233, *t*=2.211, *p*=0.030), total comorbidity scores, and use of anti-depressants (β=0.542, *t*=4.487, *p*<0.001) (Table 3).

The link of dietary vitamin D deficiency and vitamin D supplements to cardiac event-free survival

During the follow-up period (median 144 days, interquartile range 84–232 days), three patients (1.7%) died due to decompensated HF, 28 (15.8%) were hospitalized due to decompensated HF and 21 (11.9%) were hospitalized due to other cardiac-related problems.

Among patients with moderate to severe depressive symptoms (*n*=82), dietary vitamin D deficiency and no supplementation independently predicted shorter cardiac event-free survival in hierarchical Cox hazard proportional regression after controlling for age, gender, living status, body mass index, New York Heart Association functional class, total comorbidities, and use of anti-depressants. Patients with dietary vitamin D deficiency and no supplements had a 9.5-fold higher risk of cardiac events than those with dietary vitamin D adequacy and supplements (*p*=0.001). Patients with dietary vitamin D deficiency and supplements had a 7.9-time risk for having cardiac events compared to those with dietary vitamin D adequacy and supplements (*p*=0.018) (Table 4).

In contrast, there was no significant difference in cardiac event-free survival among four groups categorized by dietary vitamin D deficiency and vitamin D supplements in patients with mild depressive symptoms (*n*=95) (Figure 1).

Discussion

The most compelling finding of this study was that patients with HF who had dietary vitamin D deficiency and did not use vitamin D supplements had the highest risk for depressive symptoms and hospitalization or death due to cardiac problems compared to other groups, but only when patients

Table 3. The link of vitamin D deficiency and vitamin D supplements to depressive symptoms at six months in hierarchical linear regression, *n*=177.

Variables	Patients with mild depressive symptoms (*n*=95)						Patients with moderate to severe depressive symptoms (*n*=82)					
	Step 1			*Step 2*			*Step 1*			*Step 2*		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Age, years	–0.294	–2.959	0.004	–0.262	–2.492	0.015	–0.082	–0.717	0.476	–0.126	–1.166	0.248
Female, gender	–0.129	–1.339	0.184	–0.126	–1.305	0.196	–0.063	–0.570	0.571	–0.011	–0.113	0.910
Living with someone	–0.073	–0.645	0.520	–0.052	–0.457	0.649	–0.090	–0.796	0.429	–0.058	–0.557	0.579
Body mass index	–0.006	–0.058	0.954	0.006	0.056	0.955	–0.170	–1.477	0.144	–0.210	–1.986	0.051
NYHA class III/IV	0.134	1.360	0.178	0.103	1.025	0.309	0.330	2.912	0.005	0.233	2.211	0.030
Total comorbidity score	0.060	0.512	0.610	0.013	0.111	0.912	0.155	1.329	0.188	0.112	1.063	0.291
Use of anti-depressants	0.417	4.178	<0.001	0.345	3.206	0.002	0.267	2.456	0.016	0.205	2.060	0.043
Vitamin D adequacy and no vitamin D supplements				0.098	0.882	0.381				0.311	2.513	0.014
Vitamin D deficiency and vitamin D supplements				0.062	0.576	0.566				0.237	2.016	0.048
Vitamin D deficiency and no vitamin D supplements				0.224	1.839	0.070				0.542	4.487	<0.001
Overall	R^2=0.27, Δ in R^2=0.27 p<0.001			R^2=0.30, Δ in R^2=0.03 p=0.001			R^2=0.21, Δ in R^2=0.21 p=0.015			R^2=0.39, Δ in R^2=0.18 p<0.001		

NYHA: New York Heart Association.

Table 4. The link of vitamin D deficiency and vitamin D supplements to cardiac event-free survival in hierarchical Cox proportional hazard regression analysis, *n*=177.

	Variables		*Patients with mild depressive symptoms* (*n*=95)			*Patients with moderate to severe depressive symptoms* (*n*=82)		
			Adjusted HR	95% CI	*p*	Adjusted HR	95% CI	*p*
Step 1	Age, years		1.027	0.993–1.063	0.272	0.979	0.937–1.022	0.332
	Gender	Male	1.000			1.000		
		Female	0.544	0.184–1.611	0.272	0.716	0.296–1.736	0.460
	Living status	With someone	1.000			1.000		
		Alone	1.762	0.751–4.133	0.193	2.305	0.927–5.733	0.072
	Body mass index, kg/m^2		1.012	0.962–1.064	0.650	0.988	0.932–1.047	0.673
	NYHA	Class I/II	1.000			1.000		
		Class III/IV	2.191	0.957–5.017	0.064	0.977	0.423–2.254	0.956
	Total comorbidity score		1.050	0.853–1.292	0.648	1.064	0.830–1.364	0.625
	Use of anti-depressants		1.055	0.349–3.188	0.924	0.690	0.238–1.998	0.494
Step 2	Vitamin D adequacy and vitamin D supplements		1.000			1.000		
	Vitamin D adequacy and no vitamin D supplements		1.550	0.508–4.728	0.441	1.283	0.295–5.578	0.739
	Vitamin D deficiency and vitamin D supplements		2.063	0.722–5.891	0.176	7.857	1.416–43.59	0.018
	Vitamin D deficiency and no vitamin D supplements		0.958	0.245–3.741	0.950	9.530	2.425–37.45	0.001

CI: confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

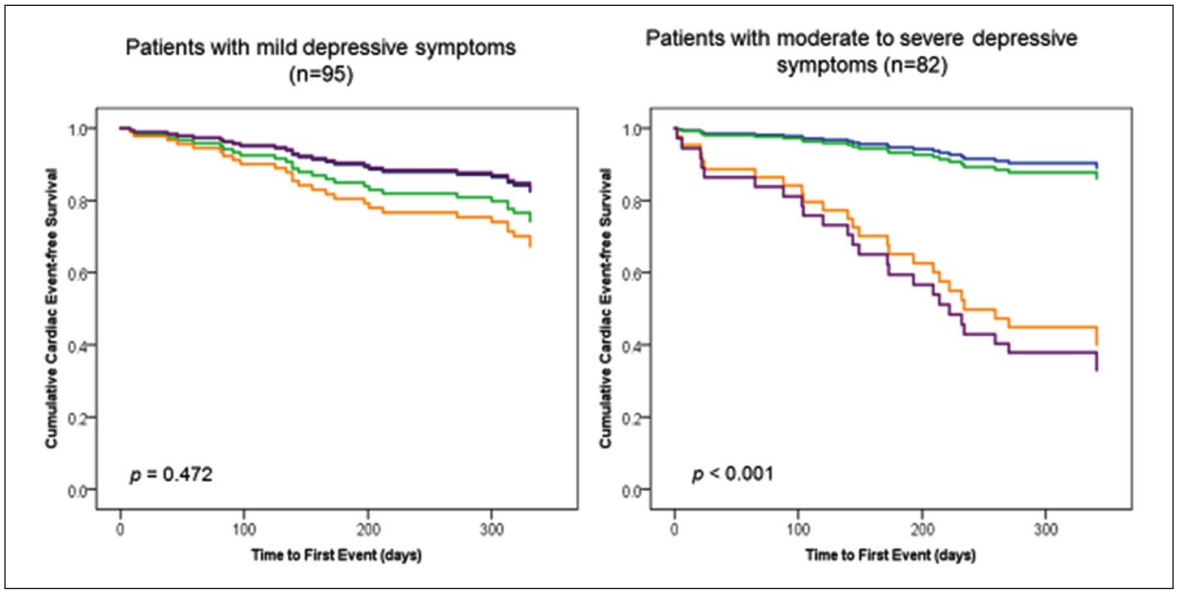

Figure 1. Adjusted cardiac event-free survival curves stratified by dietary vitamin D deficiency and use of vitamin D supplements in patients with mild and moderate to severe depressive symptoms.

had moderate to severe depressive symptoms. In addition, a group with vitamin D adequacy and no vitamin D supplements, and a group with vitamin D deficiency and vitamin D supplements were associated with greater level of depressive symptoms at six months, among HF patients with moderate to severe depressive symptoms. Our findings are consistent with those of a meta-analysis by Shaffer and colleagues[16] who found that use of vitamin D supplements was associated with reduction in depressive symptoms for patients with clinically significant depressive symptoms or a major depressive disorder. Furthermore, our study extended the current knowledge regarding the impact of vitamin D supplementation on cardiac event-free survival in patients with HF.

To date, vitamin D supplementation has been shown to decrease parathyroid hormone and inflammation,[34] but no positive effects of vitamin D supplementations on health outcomes were reported in patients with HF. Most recently, a randomized clinical trial showed that a daily vitamin D dose of 4000 IU for three years did not reduce all-cause mortality in patients with HF.[35] Therefore, randomized control trials could be recommended to determine the protective role of vitamin D supplements against severe depressive symptoms and secondary cardiac events for patients with HF who have moderate to severe depressive symptoms.

In our study, vitamin D supplementation by itself was not associated with a lower risk of depressive symptoms and cardiac hospitalization or death in patients with HF, regardless of depressive symptom severity. Particularly in patients with HF and moderate to severe depressive symptoms, adequate intake of vitamin D may play a role in protection against depressive symptoms and cardiac events. Therefore, ongoing assessment for vitamin D intake may be important for depressed patients with HF, even when they take vitamin D supplements. The most natural way to obtain vitamin D is exposing the skin to sunlight, because skin synthesis accounts for approximately 80% of vitamin D.[36] However, older adults and depressed people are likely to spend more time indoors, which then requires that vitamin D is obtained from food.[37,38] Accordingly, patients should be informed that foods high in vitamin D include fatty fish (such as salmon, tuna, and mackerel), beef liver, cheese, egg yolks, milk, yogurt, or orange juice fortified with vitamin D.[21,39] Healthcare providers should inform patients with minimal sun exposure that the optimal daily intake of vitamin D is 20–25 mcg,[38] which produces serum levels shown to prevent cardiovascular risk.[40,41]

One of unexpected findings was that anti-depressant use was associated with a higher risk of depressive symptoms in our study. Conversely, all patients in this study who were prescribed antidepressants still had depressive symptoms. Compared to the depressive symptom trajectory by Dekker and colleagues,[27] a higher proportion of patients in our study had persistent depressive symptoms but the proportion of anti-depressant use was very similar. Notably, our finding indicated that the positive association of anti-depressants with depressive symptoms was attenuated in patients with dietary vitamin D adequacy and vitamin D supplements. Previously, a combination of vitamin D supplements with anti-depressants was more effective in reducing depressive symptoms than anti-depressants alone in patients with major depressive disorder.[42,43] Randomized controlled trials would clarify the effectiveness of vitamin D supplements on depressive symptoms in patients with HF who are depressed and have dietary vitamin D deficiency.

Several limitations are recognized. Dietary vitamin D intake was used in our study, rather than serum level of vitamin D, and the possible impact of sun exposure as a confounding variable on serum level of vitamin D was not addressed in our study. Vitamin D intake and use of vitamin D supplements were measured at a single time point and may not adequately reflect the long-term dietary intake of vitamin D and vitamin D supplementation. It is known that patients with HF and depressive symptoms are more likely to have poor self-care behaviors, including lack of adherence to medication or diet.[44] Additionally, we did not consider potential seasonal variation in patients' diets, although nutrient intake was minimally changed across the four seasons in Korean adults.[45] Also, as a prospective study, the associations among vitamin D intake, vitamin D supplementation, depressive symptoms, and subsequent cardiac events do not necessarily indicate causality. Therefore, additional research is necessary to verify our findings in a larger population and across various settings. Furthermore, randomized controlled trials are necessary to provide a better understanding for the role of vitamin D against depressive symptoms and cardiac events in patients with HF.

Conclusion

This study provides additional evidence that vitamin D supplements are related to reduced depressive symptoms and cardiac events for patients with moderate to severe depressive symptoms. In addition, dietary vitamin D deficiency was associated with depressive symptoms and shorter cardiac event-free survival in patients with HF, irrespective of vitamin D supplementation. Continuous monitoring for vitamin D intake may be warranted for HF patients, especially for those with depressive symptoms, even if they take vitamin D supplements. Future research is needed which is focused on determining whether vitamin D plays an important role in preventing depressive symptoms and cardiac events among patients with HF through randomized controlled trials.

Implications for practice

- Vitamin D supplements are associated with lower depressive symptoms and reduced cardiac events for heart failure (HF) patients with moderate to severe depressive symptoms.
- Patients with vitamin D deficiency have higher risk of severe depressive symptoms and shorter cardiac event-free survival, regardless of vitamin D supplementation.
- Clinicians need to assess vitamin D intake for patients with HF, particularly for those with depressive symptoms, even if they take vitamin D supplements.
- Randomized controlled trials are suggested to determine the role of vitamin D in preventing depressive symptoms and cardiac events in patients with HF.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Zittermann A, Schleithoff SS, Tenderich G, et al. Low vitamin D status: A contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol* 2003; 41: 105–112.
2. Ameri P, Ronco D, Casu M, et al. High prevalence of vitamin D deficiency and its association with left ventricular dilation: An echocardiography study in elderly patients with chronic heart failure. *Nutr Metab Cardiovasc Dis* 2010; 20: 633–640.
3. Arroyo M, Laguardia SP, Bhattacharya SK, et al. Micronutrients in African-Americans with decompensated and compensated heart failure. *Transl Res* 2006; 148: 301–308.
4. Hughes CM, Woodside JV, McGartland C, et al. Nutritional intake and oxidative stress in chronic heart failure. *Nutr Metab Cardiovasc Dis* 2012; 22: 376–382.
5. McKeag NA, McKinley MC, Harbinson MT, et al. Dietary micronutrient intake and micronutrient status in patients with chronic stable heart failure: An observational study. *J Cardiovasc Nurs* 2017; 32: 148–155.
6. Pilz S, Marz W, Wellnitz B, 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. *J Clin Endocrinol Metab* 2008; 93: 3927–3935.
7. Zittermann A, Schleithoff SS, Gotting C, et al. Poor outcome in end-stage heart failure patients with low circulating calcitriol levels. *Eur J Heart Fail* 2008; 10: 321–327.
8. Song EK and Kang SM. The relationship of depressive symptoms and vitamin D intake to cardiac event-free survival in patients with heart failure. *J Cardiovasc Nurs* 2017; 32: 480–487.
9. Rutledge T, Reis VA, Linke SE, et al. Depression in heart failure: A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006; 48: 1527–1537.
10. Fan H, Yu W, Zhang Q, et al. Depression after heart failure and risk of cardiovascular and all-cause mortality: A meta-analysis. *Prev Med* 2014; 63C: 36–42.
11. May HT, Bair TL, Lappe DL, et al. Association of vitamin D levels with incident depression among a general cardiovascular population. *Am Heart J* 2010; 159: 1037–1043.
12. Johansson P, Alehagen U, van der Wal MH, et al. Vitamin D levels and depressive symptoms in patients with chronic heart failure. *Int J Cardiol* 2016; 207: 185–189.
13. Anglin RE, Samaan Z, Walter SD, et al. Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. *Br J Psychiatry* 2013; 202: 100–107.
14. Gowda U, Mutowo MP, Smith BJ, et al. Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. *Nutrition* 2015; 31: 421–429.
15. Li G, Mbuagbaw L, Samaan Z, et al. Efficacy of vitamin D supplementation in depression in adults: A systematic review. *J Clin Endocrinol Metab* 2014; 99: 757–767.
16. Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: A systematic review and meta-analysis of randomized controlled trials. *Psychosom Med* 2014; 76: 190–196.
17. Han C, Jo SA, Kwak JH, et al. Validation of the Patient Health Questionnaire-9 Korean version in the elderly population: The Ansan Geriatric study. *Compr Psychiatry* 2008; 49: 218–223.
18. Aquilani R, Opasich C, Verri M, et al. Is nutritional intake adequate in chronic heart failure patients? *J Am Coll Cardiol* 2003; 42: 1218–1223.
19. Ortega RM, Perez-Rodrigo C and Lopez-Sobaler AM. Dietary assessment methods: Dietary records. *Nutr Hosp* 2015; 31: S38–S45.
20. The Korean Nutrition Society. *Computer aided nutritional analysis program 4.0 for professionals*. Seoul, Korea: The Korean Nutrition Society, 2011.
21. The Korean Nutrition Society. *Dietary reference intakes for Koreans 2015*. 1st ed. Seoul, Korea: The Hanareum Publishing Co., 2015.
22. Kim JW, Lee SH, Kim JE, et al. The association between taking dietary supplements and healthy habits among Korean adults: Results from the Fifth Korea National Health and Nutritional Examination Survey (2010–2012). *Korean J Fam Med* 2016; 37: 182–187.
23. Fan X, Lee KS, Frazier SK, et al. The use of, and perceptions about, dietary supplements among patients with heart failure. *Eur J Cardiovasc Nurs* 2014; 13: 311–319.
24. Kroenke K, Spitzer RL and Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16: 606–613.
25. Spitzer RL, Kroenke K and Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary care evaluation of mental disorders. Patient Health Questionnaire. *JAMA* 1999; 282: 1737–1744.
26. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40: 373–383.
27. Dekker RL, Lennie TA, Albert NM, et al. Depressive symptom trajectory predicts 1-year health-related quality of life in patients with heart failure. *J Card Fail* 2011; 17: 755–763.
28. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; 39: 175–191.
29. Zaharias E, Cataldo J, Mackin L, et al. Simple measures of function and symptoms in hospitalized heart failure patients predict short-term cardiac event-free survival. *Nurs Res Pract* 2014; 2014: 815984.
30. Campbell RT and McMurray JJ. Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. *Heart Fail Clin* 2014; 10: 481–501.
31. Lee KS, Lennie TA, Yoon JY, et al. Living arrangements modify the relationship between depressive symptoms and

self-care in patients with heart failure. *J Cardiovasc Nurs* 2017; 32: 171–179.
32. Chung ML, Dekker RL, Lennie TA, et al. Antidepressants do not improve event-free survival in patients with heart failure when depressive symptoms remain. *Heart Lung* 2013; 42: 85–91.
33. Song EK, Moser DK, Dekker RL, et al. The impact of body mass index on the link between depressive symptoms and health outcome in patients with heart failure. *J Cardiovasc Nurs* 2015; 30: 529–536.
34. Jiang WL, Gu HB, Zhang YF, et al. Vitamin D supplementation in the treatment of chronic heart failure: A meta-analysis of randomized controlled trials. *Clin Cardiol* 2016; 39: 56–61.
35. Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): A 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur Heart J*. In press.
36. Macdonald HM, Mavroeidi A, Fraser WD, et al. Sunlight and dietary contributions to the seasonal vitamin D status of cohorts of healthy postmenopausal women living at northerly latitudes: A major cause for concern? *Osteoporos Int* 2011; 22: 2461–2472.
37. Cashman KD, Wallace JM, Horigan G, et al. Estimation of the dietary requirement for vitamin D in free-living adults ≥64 y of age. *Am J Clin Nutr* 2009; 89: 1366–1374.
38. Holick MF. Vitamin D: A D-lightful health perspective. *Nutr Rev* 2008; 66: S182–S194.
39. Institue of Medicine. *Food and Nutrition Board. Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academy Press, 2010.
40. Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol* 2010; 106: 963–968.
41. Wimalawansa SJ. Vitamin D and cardiovascular diseases: Causality. *J Steroid Biochem Mol Biol*. In press.
42. Khoraminya N, Tehrani-Doost M, Jazayeri S, et al. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Aust N Z J Psychiatry* 2013; 47: 271–275.
43. Zanetidou S, Belvederi Murri M, Buffa A, et al. Vitamin D supplements in geriatric major depression. *Int J Geriatr Psychiatry* 2011; 26: 1209–1210.
44. Kessing D, Denollet J, Widdershoven J, et al. Psychological determinants of heart failure self-care: Systematic review and meta-analysis. *Psychosom Med* 2016; 78: 412–431.
45. Kim DW, Kyung Park M, Kim J, et al. Sources of variation in nutrient intake and the number of days to assess usual intake among men and women in the Seoul metropolitan area, Korea. *Br J Nutr* 2013; 110: 2098–2107.