Vitamin D deficiency and functional response to CRT in heart failure patients

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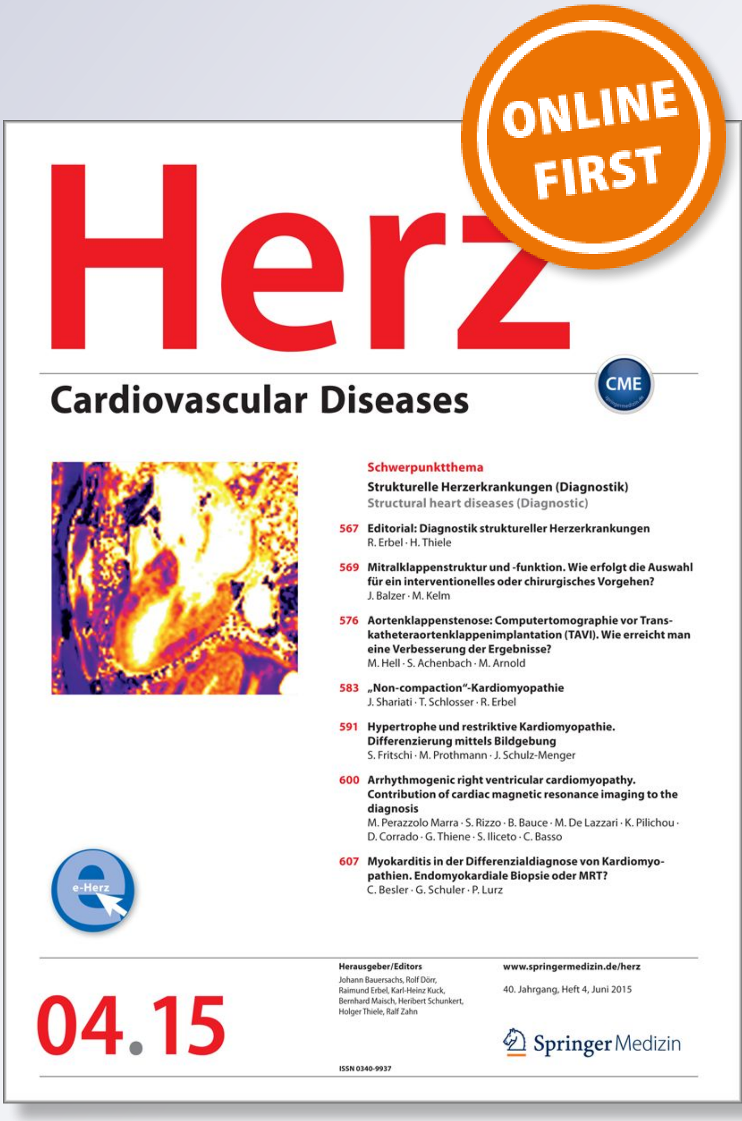

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Vitamin D deficiency and functional response to CRT in heart failure patients

Heart failure (HF) is a major public health problem with remarkable mortality and morbidity that is considered an emerging epidemic [1]. For over two decades, cardiac resynchronization therapy (CRT) has been used as a highly effective treatment in remodeling the myocardium and improving both functional capacity and survival of patients with advanced systolic HF [2]. However, almost one third of patients, referred as "nonresponders," fail to show a favorable response to this treatment [3]. The lack of response to CRT, particularly in view of the anticipated expanding indications for treatment, is an increasingly important challenge [4]. Hence, identification of factors that are associated with a poor response rate to CRT are of paramount importance [5]. Male gender, ischemic etiology of the underlying cardiomyopathy, shorter distance in baseline 6-Minute Walk Test, and presence of renal failure are among the clinical factors that contribute to the lack of response to CRT [6]. Furthermore, several electrocardiographic and echocardiographic factors have also been correlated to the lack of response, such as larger baseline size of the left ventricle and presence of nonsinus rhythm [7–9]. Additionally, some laboratory markers including high phosphorus level and high sensitivity C-reactive protein (hs-CRP) level were also shown to be associated with unfavorable response to CRT [10, 11].

An inadequate level of serum vitamin D is a global health problem and is considered a pandemic [12]. Vitamin D is recognized as a multifunctional hormone with several pleiotropic extraskeletal effects [13]. It has been implicated in enhancing immunity and cardiovascular health [13]. In cross-sectional studies, vitamin D deficiency has been associated with various cardiovascular diseases including HF [14, 15]. Vitamin D deficiency is associated with increased activity of parathormone (PTH). PTH is a vasculotoxic hormone that contributes to hypertrophy of myocytes and interstitial fibrosis, and hence can adversely affect myocardial function [16]. Vitamin D deficiency is prevalent in HF and is associated with worse functional capacity, more hospital admissions, and higher long-term mortality rates [17, 18]. Vitamin D supplement was reported to improve cardiac function in HF patients without improving the functional capacity [19].

In one study, the serum vitamin D level was found to be an independent predictor of response to CRT [20]. Given the high prevalence of vitamin D insufficiency in the geographical region covered by this heart center, we aimed to examine the possible contribution of hypovitaminosis D to the lack of response to CRT in patients with systolic HF. The primary endpoint of this study was a combination of clinical and echocardiographic response to CRT as assessed by either ≥10% (or 50 m) improvement in distance in the 6-Minute Walk Test or ≥15% reduction in the left ventricular end-systolic volume (LVESV) within 6 months of CRT implantation. We hypothesized that compared with patients who have sufficient levels of vitamin D, patients with insufficient concentrations (<30 ng/ml) are less likely to respond to CRT.

Patients and methods

The design of the study comprised a prospective longitudinal cohort of patients grouped according to their serum vitamin D concentrations. The study subjects included consecutive patients who underwent CRT implantation for managing systolic heart failure from January 2015 to January 2016 in a heart center affiliated with Tabriz University of Medical Sciences. The study was approved by the local ethics committees of the university and all patients provided written informed consent according to the Declaration of Helsinki to participate in this study. Patients were included if they fulfilled class I or IIa indication for CRT implantation according to the latest guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) [21].

The exclusion criteria were: left ventricular (LV) lead position other than the anterolateral, lateral, and posterolateral; biventricular pacing <90%; nonadherence to standard medical therapy; severe tricuspid regurgitation or mitral regurgitation in baseline echocardiography; right ventricular failure defined as tricuspid annular plane systolic excursion (TAPSE) ≤15 mm; acute coronary syndrome/coronary revascularization in the preceding 3 months; and presence of severe pulmonary artery hypertension. Additionally, we did not enroll patients if they had: a history of hypercalcemia and

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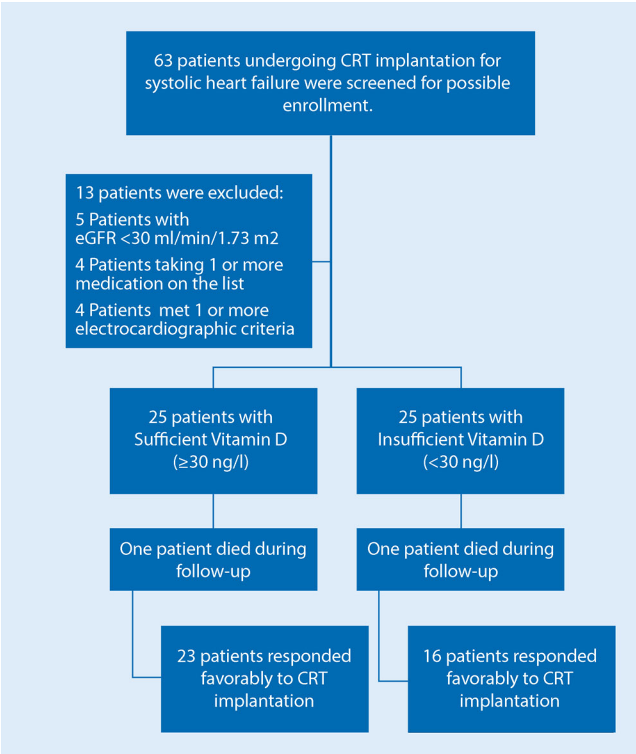

Fig. 1 ◂ Flow chart of study design. *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate

hyperparathyroidism; stage IV or higher chronic kidney disease with an estimated glomerular filtration rate (eGFR) <30 ml/min; liver dysfunction or cirrhosis; chronic obstructive pulmonary disease; consumption of medications/supplements containing vitamin D, calcium, steroids, or estrogen; history of osteomalacia or osteoporosis; history of cancer; and those who concomitantly used medications that could affect vitamin D levels, such as ketoconazole, cholestyramine, phenytoin, or phenobarbital.

Demographic and anthropometric data, New York Heart Association (NYHA) functional class, comorbidities, HF etiology (ischemic and nonischemic), and medication history were recorded for all patients prior to the implantation procedure. Electrocardiographic information was reviewed for every patient and rhythm as well as the durations of the P-R and QRS complex were recorded. Hematologic and biochemical analyses of the peripheral blood were obtained on the day of admission and hemoglobin, HbA1c, sodium, potassium, and creatinine levels were documented. Furthermore, serum concentrations of vitamin D, parathyroid hormone (PTH), and ionized calcium were also measured prior to CRT implantation.

The 6-Minute Walk Test was performed 1 week before the procedure and the distance for this test was recorded. Additionally, a comprehensive transthoracic echocardiographic examination was performed. LVESV (ml), left ventricular end-diastolic volume (LVEDV; ml), left ventricular end-diastolic diameter (LVEDD; cm), left ventricular end-systolic diameter (LVESD; cm), LV ejection fraction (LVEF), and TAPSE (mm) as well as the severity of mitral regurgitation and tricuspid regurgitation were measured and recorded prior to the implantation of CRT. All patients were implanted with a CRT device according to a standard method and programmed to DDD mode. The LV lead was placed in the coronary sinus in all cases. Right atrial and right ventricular leads were placed in the right atrial appendage and the right ventricular apex, as per routine. Appropriate lead positioning was assessed in all cases by postprocedural x-ray. Standard ICD interrogation and monitoring were done at the 1-, 3-, and 6-month follow-up for each patient. All patients received optimal medical therapy during the follow-up period. After the procedure, all patients were followed up for 6 months checking for hospital re-admission and mortality.

At the end of the 6-month follow-up, patients were re-examined for any change in their functional status. Electrocardiography, transthoracic echocardiography, and the Six-Minute Walk test were repeated. Two experienced cardiologists who were blind to the clinical and laboratory findings interpreted the echocardiographic examinations and performed all measurements. The primary endpoint for this study was the presence or the absence of response to CRT placement. Patients were considered responders if 6 months after the initiation of CRT, they were alive and had ≥15% reduction in LVESV and ≥10% (or 50 m) improvement in the 6-Minute Walk Test. Patients were grouped according to their baseline serum vitamin D concentrations: serum concentrations of ≥30 ng/ml were considered sufficient (group 1) and those with levels <30 ng/ml were considered insufficient (group 2).

Statistical analysis and sample size determination

The patient groups were labelled as "sufficient" versus "insufficient levels of vitamin D". According to values published in the geographic region of interest, the prevalence of insufficient vitamin D is approximately 50% with the age group comparable to this study. Additionally, the rate of response to CRT among the patients with symptomatic systolic HF ranges from 60 to 75%, both based on our institutional experience and experiences published by others [20]. A decrease in response from 70 to 40% was considered clinically significant. Using a web-based calculator that was provided by the University of British Columbia website, a total of 20 patients in each group was needed to achieve a power of 80%. All data were entered in a Microsoft Excel worksheet and were transferred to SPSS 24.0 (IBM®, Chicago, IL, USA.) for analysis. Cross-tabulation with chi-square analysis was used to examine categorical variables. Data are expressed as frequencies (percentage) and corresponding odds ratio with 95% confidence intervals. Numerical values were tested for normality using the Kolmogorov–Smirnov test. Variables with normal distribution were analyzed using independent *t* tests and data are expressed as mean ± standard deviation. The Mann–Whitney *U* test was used for nonparametric analysis of variables that did not have a normal distribution. One-way repeated measures analysis of variance was used to evaluate alterations in continuous variables. A multivariate regression model was constructed and variables with a *p* value less than 0.15 in univariate analysis to identify factors were independently associated with lack of response to CRT. Null hypotheses were rejected if the alpha value was <0.05.

Results

In all, 63 patients underwent CRT implantations during the study period, of whom 13 were excluded owing to chronic kidney disease, use of unpermitted medications, and echocardiographic criteria (**Fig. 1**). Subsequently, 50 patients agreed to participate and were enrolled in this study after signing an informed consent form. Of the patients, 30 were male (60%) and 20 (40%) were female. The mean age of the study population was 66 ± 12 years. There were 18 patients (36%) with a history of previous myocardial infarction. Prior to CRT implantation, 15 patients had NYHA II functional status (30%) and 35 patients (70%) had NYHA III functional status. All patients were in sinus rhythm and the duration of QRS was longer than 120 ms with left bundle branch block (LBBB) morphology. The manufacturing company of the CRT device was Medtronic (Minneapolis, MN, USA) in 40 cases and St. Jude Medical (St. Paul, MN, USA) in ten cases. The LV lead was implanted in the coronary sinus in all cases. LV lead pacing was anterolateral in three cases (6%), lateral in ten cases (20%), and posterolateral in 37 cases (74%).

CRT implantation did not result in a favorable outcome in 11 patients;

Abstract · Zusammenfassung

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Vitamin D deficiency and functional response to CRT in heart failure patients

Abstract

Background. Vitamin D deficiency has been associated with a poor outcome in patients with heart failure (HF). We examined the role of vitamin D in the response of HF patients to cardiac resynchronization therapy (CRT).
Methods. The study comprised 50 patients (30 men and 20 women) with HF undergoing CRT implantation who were prospectively enrolled. Response to CRT was defined as a combination of ≥15% reduction in left ventricular end-systolic volume (LVESV) and ≥10% improvement in the 6-Minute Walk Test within 6 months. Patients were grouped based on their levels of vitamin D prior to CRT implantation. Clinical and echocardiographic examinations were performed prior to and 6 months after the procedure.
Results. Of the patients, 11 (22%) failed to respond to CRT; two patients died within 6 months and an additional nine patients showed no improvement in the 6-Minute Walk Test and no reduction in their baseline LVESV. A comparison was made between 25 patients with sufficient levels of vitamin D and 25 patients with insufficient levels. Nine patients (36%) in the "insufficient" group and two patients (8%) in the "sufficient" group failed to respond to CRT implantation (p = 0.037).
Conclusion. Adequate serum concentrations of vitamin D play a significant role in improving the functional status of patients with systolic HF following CRT implantation.

Keywords

Systolic heart failure · Cardiac resynchronization therapy · Myocardial remodeling · Ventricular end-systolic volume · 6-Minute Walk Test

Vitamin-D-Mangel und funktionelle Antwort auf CRT bei Herzinsuffizienzpatienten

Zusammenfassung

Hintergrund. Vitamin-D-Mangel wird mit einem ungünstigen Verlauf bei Patienten mit Herzinsuffizienz in Zusammenhang gebracht. In der vorliegenden Arbeit wurde die Bedeutung von Vitamin D für die Antwort von Herzinsuffizienzpatienten auf eine kardiale Resynchronisationstherapie (CRT) untersucht.
Methoden. Die vorliegende Studie umfasste 50 Patienten (30 m., 20 w.) mit Herzinsuffizienz und CRT-Implantation, die prospektiv in die Studie aufgenommen wurden. Als Therapieansprechen auf die CRT wurde die Kombination einer Verminderung des linksventrikulären endsystolischen Volumens (LVESV) von ≥15 % und einer Verbesserung im 6-min-Gehtest von ≥10 % innerhalb von 6 Monaten definiert. Die Patienten wurden anhand ihrer Vitamin-D-Werte vor CRT in Gruppen eingeteilt. Eine klinische Untersuchung und eine Echokardiographie wurden vor und 6 Monate nach dem Eingriff durchgeführt.
Ergebnisse. Kein Therapieansprechen auf die CRT bestand bei 11 Patienten (22 %); 2 Patienten starben innerhalb von 6 Monaten und weitere 9 zeigten weder eine Verbesserung im 6-min-Gehtest noch eine Verminderung ihres Ausgangs-LVESV. Es wurden 25 Patienten mit ausreichenden Vitamin-D-Werten und 25 Patienten mit nicht ausreichenden Werten verglichen. Kein Therapieansprechen auf die CRT gab es bei 9 Patienten (36 %) in der „nicht ausreichenden" Gruppe und bei 2 Patienten (8 %) in der „ausreichenden" Gruppe (p = 0,037).
Schlussfolgerung. Ausreichende Serumkonzentrationen von Vitamin D spielen eine bedeutende Rolle bei der Verbesserung der Leistungsfähigkeit von Patienten mit systolischer Herzinsuffizienz nach CRT-Implantation.

Schlüsselwörter

Systolische Herzinsuffizienz · Kardiale Resynchronizationstherapie · Myokardiales Remodeling · Ventrikuläres endsystolisches Volumen · 6-min-Gehtest

Table 1 Demographic and medical characteristics of patients

		CRT responders		CRT nonresponders		OR	Lower CI	Upper CI	*p*
Gender	Male	22	56.4%	8	72.8%	0.49	0.11	2.11	0.489
	Female	17	43.6%	3	27.3%				
Age (years)		64.7 ± 11.2		69.6 ± 14.4		–	−13.16	3.40	0.242
BMI (kg/m²)		27.8 ± 3.6		26.1 ± 3.4		–	−0.75	4.18	0.169
Etiology	Ischemic	21	53.8%	9	81.8%	0.26	0.05	1.36	0.163
	Nonischemic	18	46.2%	2	18.2%				
Prior myocardial infarction		13	33.3%	4	36.4%	0.88	0.22	3.54	>0.99
Diabetes mellitus		15	38.5%	3	27.3%	1.67	0.38	7.29	0.724
Hypertension		20	51.3%	7	63.6%	0.60	0.15	2.39	0.515
Current smoker		5	12.8%	3	27.3%	0.39	0.08	2.00	0.351
Beta blockers		33	84.6%	10	90.9%	0.55	0.07	5.13	>0.99
Angiotensin inhibitors/blockers		36	92.3%	11	100.0%	–	–	–	>0.99
Diuretics		26	66.7%	9	81.8%	0.44	0.08	2.36	0.468
Statins		23	59.0%	7	63.6%	0.82	0.21	3.28	>0.99
Digitalis treatment		18	46.2%	8	72.8%	0.32	0.07	1.40	0.175
Antiplatelet therapy		33	84.6%	10	90.9%	0.55	0.06	5.13	>0.99
Nitrates		11	28.2%	4	36.4%	0.69	0.17	2.82	0.713
Class III antiarrhythmic drugs		5	12.8%	1	9.1%	1.47	0.15	14.09	>0.99

Mean ± standard deviation is reported for age
BMI body mass index, *CI* confidence interval, *CRT* cardiac resynchronization therapy, *OR* odds ratio

Table 2 Baseline laboratory values of patients

	CRT responders		CRT nonresponders		*p*
	M	*SD*	*M*	*SD*	
Hemoglobin (g/dl)	13.4	2.0	13.7	2.2	0.667
HbA1c[a] (%)	6.9	2.1	6.2	2.0	0.351
Serum sodium (meq/l)	141	4	140	3	0.303
Serum potassium (meq/l)	4.5	0.3	4.6	0.3	0.336
Serum creatinine (mg/dl)	1.11	0.26	1.34	0.26	0.013
eGFR[b] (ml/min/1.73 m²)	70	21	61	27	0.270
Serum vitamin D (ng/dl)	41.4	26.6	24.8	10.4	0.004
Parathormone level (ng/l)	49.9	35.3	48.9	34.0	0.936
Ionized calcium (mg/dl)	1.14	0.08	1.18	0.14	0.255

CRT cardiac resynchronization therapy, *eGFR*[b] estimated glomerular filtration rate, *SD* standard deviation, *M* mean
[a]Percent glycated hemoglobin A
[b]Estimated glomerular filtration rate calculated by MDRD formula

two patients died during the follow-up period while the remaining nine patients had either no improvement in the 6-Minute Walk Test or no reduction in LVESV 6 months after implantation. In 24 patients, NYHA II functional status improved by one class, while there was no change in the functional class of the remaining 24 patients who were alive at the end of the 6-month period. Exacerbation of HF symptoms resulting in hospital re-admission was observed in two (5.1%) of the responders and four (44.4%) of the nonresponders during the follow-up period (p = 0.008). Responders were demographically similar to nonresponders, as there was no difference between the two groups based on gender, age, body habitus, smoking, ischemic vs. non-ischemic cause of cardiomyopathy, and frequency of hypertension, diabetes, or hyperlipidemia (**Table 1**). However, serum creatinine levels were significantly higher among nonresponders (1.34 ± 0.26 mg/dl) compared with 1.11 ± 0.26 mg/dl in responders. **Table 2** shows the laboratory values of the patients according to their clinical response to CRT.

Additionally, the type of CRT device was associated with a significant difference in response to the treatment. Interestingly, serum concentrations of vitamin D were 41.4 ± 26.6 ng/ml, significantly higher than 24.8 ± 10.4 ng/ml in nonresponding patients (p = 0.004).

Patients were divided into two equal groups ($N = 25$) based on having sufficient (≥30 ng/ml) or insufficient (<30 ng/ml) concentrations of vitamin D. **Table 3** shows the vitamin D level of patients. Insufficient vitamin D levels were more common in patients with ischemic etiology of HF (p = 0.042). As expected, the PTH level was also higher in patients with insufficient levels of vitamin D (p = 0.011). During the follow-up period, two patients died, one from each group. At the 6- month follow-up, patients showed a significant improvement in the Six-Minute Walk Test (330 ± 147 vs. 218 ± 103 m, $p < 0.001$). The QRS duration also significantly decreased from 156 ± 12 ms before CRT implantation to

Table 3 Patient plasma concentrations of vitamin D

		Sufficient vitamin D (≥ 30 ng/l)		Insufficient vitamin D (< 30 ng/l)		OR	Lower CI	Upper CI	*p*
Gender	Male	13	52.0%	17	68.0%	0.51	0.16	1.61	0.387
	Female	12	48.0%	8	32.0%				
Age (years)	–	63.3 ± 12.2		68.2 ± 11.2		–	−11.66	1.98	0.160
BMI (kg/m^2)	–	27.9 ± 4.1		27.0 ± 3.2		–	−1.22	2.92	0.414
Etiology	Ischemic	11	44.0%	19	76.0%	0.248	0.074	0.833	0.042
	Nonischemic	14	56.0%	6	24.0%				
Prior myocardial infarction		5	20.0%	12	48.0%	0.27	0.08	0.95	0.072
Diabetes mellitus		10	40.0%	8	32.0%	1.42	0.44	4.52	0.769
Hypertension		11	44.0%	16	64.0%	0.44	0.14	1.38	0.256
Current smoker		4	16.0%	4	16.0%	1.00	0.22	4.54	1.000
Beta-blockers		20	80.0%	23	92.0%	0.35	0.06	1.99	0.417
Angiotensin inhibitors/blockers		23	92.0%	24	96.0%	0.48	0.04	5.65	1.000
Diuretics		17	68.0%	18	72.0%	0.83	0.25	2.78	1.000
Statins		12	48.0%	18	72.0%	0.36	0.11	1.16	0.148
Digitalis treatment		11	44.0%	15	60.0%	0.52	0.17	1.61	0.396
Antiplatelet therapy		20	80.0%	23	92.0%	0.35	0.06	1.99	0.417
Nitrates		8	32.0%	7	28.0%	1.21	0.36	4.07	1.000
Class III anti-arrhythmic drugs		1	4.0%	5	20.0%	0.17	0.02	1.55	0.189
Laboratory value		*Sufficient vitamin D*		*Insufficient vitamin D*		*Diff.*	*Lower CI*	*Upper CI*	*p*
Hemoglobin (g/dl)		13.4 ± 1.8		13.6 ± 2.3		−0.20	−1.38	0.98	0.728
HbA1c[a] (%)		7.1 ± 2.1		6.4 ± 2.1		0.70	−0.48	1.89	0.239
Sodium (meq/l)		141 ± 4		141 ± 3		−0.44	−2.48	1.60	0.665
Potassium (meq/l)		4.5 ± 0.3		4.5 ± 0.3		0.03	−0.15	0.21	0.756
Creatinine (mg/dl)		1.12 ± 0.26		1.21 ± 0.28		−0.09	−0.25	0.06	0.236
eGFR[b] (ml/min/1.73 m^2)		72 ± 22		63 ± 22		8.8	−3.84	21.44	0.168
Parathormone (ng/l)		37.3 ± 18.3		62.0 ± 42.6		−24.68	−43.32	−6.04	0.011
Ionized calcium (mg/dl)		1.14 ± 0.14		1.16 ± 0.09		−0.03	−0.08	0.03	0.340

BMI body mass index, ***CI*** confidence interval, ***Diff***. difference, ***OR*** odds ratio, ***eGFR*** estimated glomerular filtration rate
[a]Percent glycated hemoglobin A
[b] Estimated glomerular filtration rate calculated by MDRD formula

143 ± 16 ms after CRT implantation ($p <$ 0.001).

Overall clinical outcome of patients was favorable in patients with sufficient levels of vitamin D. Improvement in NYHA functional class and in the 6-Minute Walk Test was more common in patients with sufficient vitamin D level ($p = 0.046$ and 0.023, respectively). **Table 4** summarizes the echocardiographic findings and clinical outcome of patients according to their vitamin D levels. Multivariate analysis was performed using all variables that had a strong trend in contributing to the lack of response to CRT. These variables included serum concentrations of creatinine and vitamin D grouping. The presence of ischemic etiology was forced into the equation because of its strong historical association with the lack of response to CRT. By step-wise removal of the least significant factors, an insufficient level of vitamin D was only significant when the response rate was adjusted to serum creatinine level. After adjusting to serum concentrations of creatinine, an insufficient level of vitamin D was associated with a 6.5-fold increase in the likelihood for the lack response to CRT ($p = 0.029$; **Table 5**).

Discussion

In this study, we prospectively examined 50 patients who underwent CRT implantation. In accordance with previous studies in our region [22], vitamin D inadequacy was found to be very common and was observed in 50% of patients. Adequate levels of vitamin D were associated with "response" to CRT and improvement in NYHA functional status. Of our patient population, 80% had a class-I indication for CRT, and the remaining 20% all had sinus rhythm and LBBB with QRS duration between 140 and 150 ms. This could explain the better response rates in this report, as patients with non-LBBB pattern/nonsinus rhythms are expected to benefit less from CRT. This is the second study that has focused on the potential effect of vitamin D in HF patients receiving CRT. Sunman et al. evaluated the vitamin D level prior to CRT implantation in 57 patients. They reported higher levels of vitamin D in

Table 4 Clinical outcome and echocardiographic findings[a]

	Sufficient vitamin D (≥ 30 ng/l)		Insufficient vitamin D (< 30 ng/l)		OR	Lower CI	Upper CI	*p*
Improvement of NYHA functional class	16	64.0%	8	32.0%	0.27	0.08	0.85	0.046
Improvement in severity of MR	10	40.0%	7	28.0%	1.71	0.53	5.6	0.551
Improvement in severity of TR	4	16.0%	1	4.0%	0.22	0.02	2.11	0.349
Hospital mortality	1	4.0%	1	4.0%	1.00	0.06	16.93	1.000
Exacerbation of HF	5	20.0%	1	4.0%	0.17	0.02	1.54	0.188
≥50 m improvement in 6-MWT	23	92.0%	16	64.0%	11.50	1.31	101.18	0.023
Echocardiographic responses	*Before*	*After*	*Before*	*After*	*Mean square*		*F*	*p*
LVEDV (ml)	178 ± 51	147 ± 55	191 ± 62	168 ± 65	6,818		1.055	0.310
LVESV (ml)	133 ± 43	103 ± 51	145 ± 55	126 ± 62	7,004		1.33	0.254
LVEDD (cm)	6.2 ± 0.7	5.9 ± 0.9	6.5 ± 0.8	6.2 ± 0.8	1.98		1.69	0.200
LVESD (cm)	5.1 ± 0.8	4.4 ± 1.2	5.4 ± 1.0	5.7 ± 3.9	15.12		2.86	0.098
LVEF	24 ± 6%	32 ± 10%	23 ± 7%	28 ± 13%	123.76		0.94	0.337
TAPSE	18.5 ± 1.7	18.4 ± 3.1	17.7 ± 2.0	17.3 ± 3.4	23.45		2.39	0.129
QRS complex duration (ms)	159 ± 13	144 ± 20	153 ± 10	141 ± 10	444.4		1.63	0.208

CI confidence interval, *HF* heart failure, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEDD* left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *MR* mitral regurgitation, *6-MWT* 6-Minute Walk Test, *NYHA* New York Heart Association, *OR* odds ratio, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation
[a]Based on sufficient plasma concentrations (≥30 ng/l) of vitamin D measured before and after resynchronization therapy

the responder group. They also reported a 40% nonresponse rate in their population, which could be attributed to the inclusion of patients with milder indications for CRT (those with atrial fibrillation and non-LBBB morphology). Patients with HF secondary to an ischemic etiology more commonly had inadequate vitamin D levels compared with those with nonischemic causes. However, our data are not suggestive of any association between the ischemic etiology of HF and vitamin D-mediated response to CRT.

Pleiotropic effects of vitamin D have been the subject of much interest, as vitamin D deficiency has been linked to various conditions including autoimmune disorders, malignancies, hypothyroidism [22], coronary artery disease, and HR [23]. The vitamin D receptor (VDR) signaling system has antihypertrophic activity in myocardium [24]. Previous studies indicate a high prevalence of vitamin D deficiency in patients with HF and its association with severe limitations in daily activity [25–27]. Mortality is also higher in HF patients with lower vitamin D levels [28]. Several plausible mechanisms could account for the observed association between inadequate vitamin D and HF. Vitamin D is an inhibitor of the renin–angiotensin–aldosterone system (RAAS) [29]. Overactivity of the RAAS leads to fibrosis, hypertrophy, and myocardial remodeling [29]. Therefore, reduced vitamin D levels could contribute to the progression of HF. Besides, low levels of vitamin D are associated with insulin resistance, diabetes, and obesity [30].

Local and systemic inflammatory responses are associated with reduced response rates to CRT. The risk of subsequent death or HF hospitalizations has been higher in patients who have elevated levels of hs-CRP compared with those in whom hs-CRP concentrations are low or undetectable [11]. In another study, an inverse relation was observed between insufficient levels of vitamin D and CRP level as a marker of inflammation [31]. Furthermore, anti-inflammatory effects are described for vitamin D, as it directly acts on matrix metalloproteinase (MMP) and its inhibitors, thereby contributing to regulation of extracellular matrix turnover [32]. The adverse effects of inadequate vitamin D levels may have led to a suboptimal response to CRT in our patients.

It should be noted that the precursor for vitamin D is hydroxylated by 25-hydroxylase enzyme located in the epidermis through exposure to the ultraviolet rays in sunlight. It is possible that patients with poorer general health and hence limited outdoor activities and exposure to sunlight have lower vitamin D concentrations compared with their healthier counterparts. Several studies have evaluated factors involved in the lack of desirable response to CRT [4–6, 33]. The second stage of vitamin D hydroxylation takes place in the kidneys, and therefore the amount of active vitamin D (1, 25 hydroxyl cholecalciferol), D3, is significantly reduced in patients with chronic kidney disease. In the present study, kidney function was found to be an independent predictor of response to CRT, which is in accordance with previous reports [34]. Although this study excluded all patients with stage 4 or higher kidney insufficiency (eGFR <30 ml/min/1.73 m^2), even in all the included subjects, the serum creatinine concentrations were significantly higher among the patients who failed to respond to CRT. Serum creatinine levels remain a significant predictor of response to CRT placement.

In addition to lower levels of serum vitamin D, there is increased activity of

Table 5 Multivariate analysis for role of vitamin D deficiency and etiology of cardiomyopathy in lack of response to CRT[a]

	Variables	Coefficient	SE	p	OR	Lower CI	Upper CI
Step 1	Ischemic/nonischemic	−0.307	0.994	0.757	0.74	0.105	5.162
	Insufficient/sufficient	−1.671	0.916	0.068	0.19	0.031	1.131
	Serum creatinine (mg/dl)	−2.939	1.572	0.062	0.05	0.002	1.154
	Constant	6.151	2.092	0.003	469.34	–	
Step 2	Insufficient/sufficient	−1.751	0.883	0.047	0.17	0.031	0.980
	Serum creatinine (mg/dl)	−3.094	1.494	0.038	0.05	0.002	0.847
	Constant	6.175	2.078	0.003	480.59	–	
Step 3	Insufficient/sufficient	−1.867	0.847	0.027	0.155	0.029	0.813
	Constant	2.442	0.737	0.001	11.500	–	

CI confidence interval, *CRT* cardiac resynchronization therapy, *OR* odds ratio, *SE* standard error
[a]Step 1 includes all three factors and the least significant factor is removed in each additional step. Insufficient level of vitamin D set at concentrations lower than 30 ng/dl

PTH in patients with suboptimal renal function, which is known to have adverse cardiovascular effects [16]. Some attribute the lower response rate to CRT to higher PTH levels. On the other hand, vitamin D deficiency is also associated with elevated concentrations of phosphorus in the serum. In a recent study, serum phosphorus levels were significantly lower in the group of patients with favorable response compared with the group with no response (3.3 ± 0.2 mg/dl vs. 3.7 ± 0.4 mg/dl) [10].

Limitations

The study is limited by the relatively small number of patients. Additionally, the study took place in a region with a high prevalence of vitamin D insufficiency. Although the relatively higher prevalence of vitamin insufficiency assisted with the power of the statistical analysis, the clinical importance of the observation remains uncertain in other regions where hypovitaminosis D is not that common. Vitamin D insufficiency may be an indicator of poor general health, which could potentially restrict the benefits of supplement therapies. Additionally, we only assessed the 6-Minute Walk Test as a clinical index of response to CRT. Use of sophisticated methods with more objective outputs such as cardiopulmonary exercise test, which allows carbon dioxide production to be measured and exercise oscillatory breathing to be assessed, would have added information on functional response to CRT.

Conclusion

We conclude that while CRT remains an effective treatment for a large proportion of patients with advanced HF, insufficient concentrations of serum vitamin D along with elevated levels of creatinine are associated with reduced rates of response to such treatment. Whether vitamin D replenishment could be used to increase the rate of response to CRT, particularly through assessment of cardiopulmonary exercise tests, remains an area for further research.

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Compliance with ethical guidelines

Conflict of interest. A. Separham , L. Pourafkari, B. Kazemi, Y. Haghizadeh, F. Akbarzadeh, M. Toufan, H. Sate, and N.D. Nader declare that they have no competing interests.

The study was approved by the local ethics committees of the university and all patients provided written informed consent according to the Declaration of Helsinki to participate in this study.

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