Turk Kardiyol Dern Ars 2016;44(8):670-676 doi: 10.5543/tkda.2016.28848

ORIGINAL ARTICLE

Vitamin D levels predict the response to cardiac resynchronization therapy in patients with systolic heart failure

Vitamin D düzeyi sistolik kalp yetersizliği olan hastalarda kardiyak resenkronizasyon tedavisine yanıtı öngörmektedir

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ABSTRACT

Objective: The aim of this study was to examine the relationship between vitamin D levels in patients with heart failure (HF) and response to cardiac resynchronization therapy (CRT).

Methods: We studied 57 patients (mean age: 60.47±13.09 years) with New York Heart Association Class II or III heart failure, QRS duration ≥120 milliseconds, and ejection fraction <35% (mean: 27.1±4.4%) who underwent CRT. All patients were taking optimal medical treatment for HF. Patients were classified as CRT responders if they had >15% decrease in left ventricular end-systolic volume at 6 months compared with baseline measurements. Vitamin D levels were evaluated before CRT implantation with ELISA.

Results: Of the 57 patients, 34 patients (59.6%) were classified as responders and 23 patients (40.4%) were classified as non-responders. Baseline features, laboratory findings, and echocardiographic characteristics were nearly the same in both groups. High vitamin D level was detected in responder group compared to non-responder group (26.17±7.5 *vs* 21.15±5.9; p=0.009). Age, hypertension, diabetes mellitus, ischemic cardiomyopathy, QRS morphology and duration, and levels of B-type natriuretic peptide (BNP) and vitamin D were associated with CRT response in our study population. In multivariate regression analysis, preimplantation QRS duration, and BNP and vitamin D levels remained independent predictors (QRS duration Odds ratio [OR]: 1.047, CI: 1.019–1.417, p=0.006; BNP OR: 0.997, 95% CI: 0.994–0.999, p=0.029; vitamin D OR: 1.121, 95% CI: 1.011–1.242, p=0.030).

Conclusion: In the present study, preimplantation level of vitamin D was found to be predictor of response to CRT, independent of BNP.

ÖZET

Amaç: Çalışmamızın amacı kalp yetersizliği (KY) olan hastalarda vitamin D düzeyi ile kardiyak resenkronizasyon tedavisine (KRT) cevap arasında ilişki olup olmadığını araştırmaktır.

Yöntemler: Çalışmaya, NYHA sınıf II-III, QRS süresi ≥120 msn, ejeksiyon fraksiyonu <%35 (ortalama %27.1±4.4) olan ve KRT uygulanan 57 (ortalama yaş 60.47±13.09 yıl) KY hastası alındı. Tüm hastalar KY açısından uygun tedavi alıyordu. Tedavi öncesine göre altıncı aydaki sol ventrikül sistol sonu hacmi >%15 azalan hastalar KRT'ye yanıt vermiş kabul edildi. Vitamin D düzeyleri KRT öncesi ELISA yöntemiyle ölçüldü.

Bulgular: Elli yedi hastadan 34'ü (%59.6) KRT'ye yanıt verdi, 23'ü (%40.4) KRT'ye yanıt vermedi. Bazal özellikler, laboratuvar bulguları ve ekokardiyografik veriler yanıt veren ve vermeyen hasta gruplarında benzerdi. Vitamin D düzeyi, yanıt vermeyen gruptaki hastalara göre yanıt veren grupta yüksek bulundu (26.17±7.5 ve 21.15±5.9; p=0.009). Çalışmamızda yaş, hipertansiyon, diyabetes mellitus, iskemik kardiyomiyopati, QRS morfolojisi ve süresi, vitamin D ve B-tipi natriüretik peptid (BNP) düzeyleri KRT'ye yanıt ile ilişkili bulundu. Çok değişkenli regresyon analizinde QRS süresi, BNP ve vitamin D düzeyleri bağımsız öngördürücüler olarak bulundu [QRS süresi: odds oranı (OO) 1.047 (güven aralığı - GA: 1.019–1.417), p=0.006; BNP OO: 0.997 (GA: 0.994–0.999), p=0.029; vitamin D OO: 1.121 (GA: 1.011–1.242), p=0.030].

Sonuç: Çalışmamızda işlem öncesi bakılan vitamin D düzeyi, BNP'den bağımsız olarak KRT'ye yanıtın bir öngördürücüsü olarak bulunmuştur.

Received: May 12, 2016 *Accepted:* September 28, 2016

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Heart failure (HF) is a major medical problem that is associated with significant rates of morbidity and mortality, hospitalization, and healthcare costs. Prognosis of patients remains poor despite advances in medical management. HF is also a progressive disease, involving activation of various neurohormonal systems and the sympathetic nervous system, which in the long term are responsible for pathological cardiac remodeling and disease progression.[1] Cardiac resynchronization therapy (CRT) is a valuable treatment option that is reducing both morbidity and mortality for patients with severe HF and left ventricular (LV) conduction disturbances.[2] Variety of parameters have been reported to be predictors of CRT response; however, lack of response to CRT has been reported in up to 30% to 40% of patients, necessitating novel predictors and treatment options.[3,4] One of the biomarkers to have emerged recently is Vitamin D and its potential role in various cardiovascular disorders, including HF.

Vitamin D is a hormone that is an actor in calcium-phosphorus metabolism and also has extraskeletal effects. Growing evidence suggests that vitamin D deficiency in HF is not a negligible laboratory finding and that there may be an intense association between these 2 common clinical entities. In the cardiovascular system, vitamin D regulates the renin-angiotensin aldosterone system (RAAS), inhibits vascular smooth muscle proliferation, and suppresses cardiac hypertrophy and hypercontractility.[5] Furthermore, experimental and epidemiological evidence has emphasized that vitamin D deficiency plays an important role in various cardiac diseases.[6] It was discovered that HF patients have low vitamin D concentrations, and this has been associated with poor cardiac reserve.[7] Moreover, vitamin D-deficient patients had worse LV function, and cardiovascular events were negatively affected by vitamin D level.[8] However, there was no evidence for role of vitamin D level in patients with CRT. In addition, predictive role of preimplantation vitamin D level remains unclear. Present study was an effort to determine whether vitamin D level correlates with CRT response in patients with HF.

METHODS

Study patients

Fifty-seven patients who received CRT were prospectively recruited between December 2010 and February 2011. Inclusion criteria included symptomatic New York Heart Association (NYHA) Class II or III HF, ejection fraction (EF) of <35%, and QRS duration of ≥120 milliseconds in form of bundle branch block or intraventricular conduction delay despite optimal pharmacological therapy. Following baseline characteristics were recorded: patient demographics (age and sex), QRS duration (ms), etiology of cardiomyopathy (ischemic or non-ischemic), medical history of hypertension, diabetes mellitus, current smoking, chronic obstructive pulmonary disease, atrial fibrillation (AF), and medication profile, including use of beta-blocker, angiotensin-converting enzyme inhibitor (ACEI), spironolactone, digoxin, or diuretics. Patients were excluded if they had clinical diagnosis of recent (≤30 days) acute coronary syndrome, acute decompensation of HF, revascularization procedure, or surgery. In addition, patients with hyperparathyroidism or hypercalcemia, nephrolithiasis, osteoporosis, chronic kidney disease, metastatic or advanced cancer, or current use of drugs that affect metabolism of vitamin D, such as vitamin D, corticosteroids, parathyroid hormone (PTH), androgen, or estrogen were excluded from the study. The study protocol was approved by the ethics committee, and written informed consent was obtained from all patients.

Abbreviations:

ACEI	*Angiotensin-converting enzyme inhibitor*
AF	*Atrial fibrillation*
BNP	*B-type natriuretic peptide*
CRT	*Cardiac resynchronization therapy*
EF	*Ejection fraction*
ELISA	*Enzyme-linked immunosorbent assay*
HF	*Heart failure*
LV	*Left ventricle*
LVES	*Left ventricular end-systolic*
LVED	*Left ventricle end-diastolic*
MMP	*Matrix metalloproteinase*
OR	*Odds ratio*
PRA	*Plasma renin activity*
PTH	*Parathyroid hormone*
RAAS	*Renin-angiotensin aldosterone system*
RV	*Right ventricle*
TIMP	*Tissue inhibitors of metalloproteinase*

Echocardiographic examination

Serial echocardiography was performed before and after CRT implantation to assess degree of LV reverse remodeling and change in cardiac function. LV end-systolic (LVES) volume, LV end-diastolic (LVED) volume, and EF were assessed using Simpson's rule. Severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in conventional parasternal long axis and apical 4-chamber

images. Patients were classified as CRT responders if they were alive and had >15% decrease in LVES volume compared with baseline measurements.

Pacemaker implantation

LV lead was implanted in the coronary sinus in all cases to achieve permanent epicardial stimulation as previously described.[9] Final lead position was assessed using postoperative chest X-ray in anteroposterior and lateral views. Right ventricular (RV) lead was implanted in the apex in all patients. Right atrium lead was then implanted in the right atrial appendage. CRT device and lead implantations were completed without major complications. CRT devices and leads used were manufactured by Medtronic, Inc. (Minneapolis, MN, USA) and Biotronik SE & Co. KG (Berlin, Germany). Devices were programmed with pacing mode DDD to maximize biventricular pacing. Re-evaluation of coronary-sinus lead position, pacing mode, and programming of timing intervals was performed 1, 3, and 6 months after implantation.

25-hydroxy vitamin D measurement

Level of 25-hydroxy (OH) vitamin D was measured using enzyme-linked immunosorbent assay test kits (DRG Diagnostics GmbH, Marburg, Germany) with dynamic range of 2.9–130 ng/mL. Intra- and inter-assay precision were 4.7% and 10.2 %, respectively.

Statistical analysis

Statistical analyses were performed using SPSS statistical software, version 20 (IBM Corp., Armonk, NY, USA). All variables were examined with regard to distributional properties using Shapiro-Wilk test, visual inspection, and assessment of kurtosis and skew. Normally distributed continuous variables were analyzed using Student's t-test and expressed as mean±SD. Abnormally distributed continuous variables were analyzed using Mann-Whitney U test and expressed as median (min-max). Categorical variables were presented as percentages and analyzed using chi-square test or Fisher's exact test. Univariate analysis of baseline variables was performed initially to investigate association between covariates and incidence of non-responders. Then, multivariate analysis (backward logistic regression) was performed using variables with p value ≤0.25 in univariate analysis. P value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Total of 57 patients (median age: 62 years [range: 23–83 years]; 66.7% men) who were referred to center for CRT device implantation were enrolled in the study. All patients received biventricular implantable cardioverter defibrillator. There was no difference in age, gender, risk factors, or echocardiographic features (EF, end-systolic volume, or mitral regurgitation). There were significant differences in QRS morphology. Left bundle branch block morphology was more frequently seen in responder group (p=0.031). Sinus rhythm was present in 53 cases, chronic AF in 4 patients, and QRS duration ranged from 120 to 230 milliseconds (mean: 160±25.3 ms). LV lead was implanted in lateral-posterolateral (n=50) or anterolateral (n=7) branch of cardiac venous system. The RV lead was implanted at RV apex in all patients. Baseline characteristics of the study population are provided in Table 1.

Follow-up

After CRT implantation, QRS shortening was significantly greater among responders than non-responders (22±21 ms vs 9±14 ms; p=0.014). Improvement in NYHA class >1 was also more common in responders than non-responders (73.5% vs 30.4%; p<0.001). In addition to clinical improvement, significant LV reverse remodeling was only observed in responder group, with mean decrease in LVES volume from 130 mL (range: 81–248 mL) to 107 mL (range: 40–213 mL) (p<0.001), and mean increase in EF from 27.3±5.4% at baseline to 35.3±7.8% at 6-month follow-up (p<0.001). There was significant worsening in cardiac dimensions and systolic function in non-responder group: LVES volume increase from 130 mL (range: 81–248 mL) to 135 mL (range: 71–260 mL) (p=0.510) and EF change from 26.7±23% to 27.3±3.8% (p=0.695).

Vitamin D and predictors of response to cardiac resynchronization therapy

Mean vitamin D level was 24.2±7.20 ng/dL and medial B-type natriuretic peptide (BNP) level was 347 pg/mL (range: 100–1825 pg/mL). Vitamin D values were significantly higher in responder group compared with non-responder group (26.17±7.5 vs 21.15±5.9; p=0.009). Univariate analysis dem-

onstrated that age, hypertension, diabetes mellitus, ischemic cardiomyopathy, QRS morphology, preimplantation QRS duration and levels of vitamin D and BNP are potential covariates. We performed multivariate analysis using covariates that showed significance in univariate analysis. After adjustment of covariates, preimplantation QRS duration and BNP and vitamin D levels remained independent predictors (QRS duration OR: 1.047, CI: 1.019–1.417, p=0.006; BNP OR: 0.997, 95% CI 0.994–0.999, p=0.029; vitamin D OR: 1.121, 95% CI 1.011-1.242, p=0.030). Detailed results of logistic regression analysis are presented in Table 2.

DISCUSSION

The present study was evaluation of predictive value of preoperative vitamin D level on CRT response in HF patients. Findings indicated that vitamin D level was statistically significantly predictive for responders to CRT. Though statistical results were only borderline significant, this is the first study to show an association between vitamin D level and CRT response in patients with HF.

Several clinical studies have demonstrated high prevalence of vitamin D deficiency in patients with HF, as well as inverse correlation between serum level

Table 1. Baseline characteristics of study population

Variables	All (n=57)	Nonresponders (n=23)	Responders (n=34)	*p*
Age (years)	62 (23–83)	58 (23–75)	64 (39–83)	0.195
Gender (female), n (%)	19 (33.3)	8 (34.8)	11 (32.4)	0.849
Hypertension, n (%)	44 (77.2)	20 (87.0)	24 (70.6)	0.148
Current smoker, n (%)	18 (31.6)	7 (30.4)	11 (32.4)	0.879
Diabetes mellitus, n (%)	12 (21.1)	7 (30.4)	5 (14.7)	0.193
NYHA classification (II/III)	5/52	2/21	3/31	1.000
Atrial fibrillation/sinus rhythm	4/53	1/22	3/31	0.641
Left ventricular ejection fraction (%), Mean±SD	27.1±4.42	26.8±2.31	27.3±5.43	0.628
Left ventricular end-systolic volume (mL)	130 (71–302)	130 (81–248)	130 (71–302)	0.536
Ischemic cardiomyopathy, n (%)	21 (36.8)	11 (47.8)	10 (29.4)	0.157
LV lead position (lateral-posterolateral/anterolateral)	50/7	20/3	30/4	1.000
QRS morphology (LBBB/non-LBBB)	49/8	17/6	32/2	0.051
Preimplantation QRS duration (ms), Mean±SD	160.6±25.34	153.4±22.99	165.5±25.99	0.075
BNP level (pg/ml)	347 (100–1825)	642 (114–1825)	252 (100–952)	0.015
Vitamin D level (ng/ml), Mean±SD	24.2±7.20	21.1±5.91	26.2±7.50	0.009
Mitral regurgitation (grade 1/2/3/4)	19/27/11/0	6/12/5/0	13/15/6/0	0.633
ACEI/ARB, n (%)	57 (100)	23 (100)	34 (100)	
Beta-blocker, n (%)	57 (100)	23 (100)	34 (100)	
Loop diuretic, n (%)	53 (93.0)	23 (100)	30 (88.2)	0.140
Spironolactone, n (%)	33 (57.9)	12 (52.2)	21 (61.8)	0.472
Digoxin, n (%)	40 (70.2)	13 (56.5)	27 (79.4)	0.064
Serum creatinine (mg/dL)	0.8±0.13	0.9±0.14	0.8±0.12	0.408
Calcium (mg/dL)	9.3±0.62	9.3±0.46	9.3±0.71	0.918
Phosphorus (mg/dL)	3.7±0.74	3.7±0.78	3.7±0.73	0.905
Albumin	4.2±0.37	4.1±0.37	4.3±0.36	0.671

NYHA: New York Heart Association; LV: Left ventricle; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers; BNP: B-type natriuretic peptide; LBBB: Left bundle branch block; SD: Standard deviation.

Table 2. Multivariate logistic regression analysis (backward elimination)

Variables	B	Exp (B)	*p*	95% CI	
				Lower	Upper
Age	0.068	1.071	0.066	0.996	1.151
Hypertension	-1.525	0.218	0.280	0.014	3.470
Diabetes mellitus	-0.627	0.534	0.559	0.065	4.380
Ischemic cardiomyopathy	0.012	1.012	0.989	0.179	5.730
QRS morphology	-1.899	0.150	0.119	0.014	1.628
Preimplantation QRS duration	0.043	1.043	0.016	1.008	1.080
BNP level	-0.002	0.998	0.085	0.995	1.000
Vitamin D level	0.112	1.118	0.054	0.998	1.253
2nd step					
Age	0.068	1.071	0.058	0.998	1.149
Hypertension	-1.519	0.219	0.257	0.016	3.028
Diabetes mellitus	-0.630	0.533	0.549	0.068	4.187
QRS morphology	-1.895	0.150	0.108	0.015	1.513
Preimplantation QRS duration	0.042	1.043	0.015	1.008	1.080
BNP level	-0.002	0.998	0.084	0.995	1.000
Vitamin D level	0.112	1.118	0.052	0.999	1.252
3rd step					
Age	0.067	1.069	0.057	0.998	1.146
Hypertension	-1.631	0.196	0.215	0.015	2.579
QRS morphology	-1.855	0.156	0.113	0.016	1.548
Preimplantation QRS duration	0.043	1.044	0.014	1.009	1.080
BNP level	-0.002	0.998	0.054	0.995	1.000
Vitamin D level	0.111	1.117	0.052	0.999	1.249
4th step					
Age	0.041	1.042	0.138	0.987	1.099
QRS morphology	-2.058	0.128	0.072	0.014	1.200
Preimplantation QRS duration	0.045	1.046	0.008	1.012	1.082
BNP level	-0.003	0.997	0.035	0.995	0.999
Vitamin D level	0.123	1.131	0.031	1.011	1.265
Last step					
QRS morphology	-1.805	0.165	0.100	0.019	1.417
Preimplantation QRS duration	0.046	1.047	0.006	1.013	1.081
BNP level	-0.003	0.997	0.029	0.994	0.999
Vitamin D level	0.114	1.121	0.030	1.011	1.242

BNP: B-type natriuretic peptide; CI: Confidence interval

of vitamin D and worsening left ventricular function and disease severity.[10–12] Liu et al. reported that lower vitamin D levels were associated with higher level of BNP and higher plasma renin activity (PRA), as well as increased HF hospitalization and overall higher incidence of all-cause mortality. In this study, low level of vitamin D was identified as independent risk factor for HF hospitalization and mortality.[13] Potential benefit of vitamin D supplementation in patients with HF has been an area of significant research interest.

Moreover, it has been determined that in patients with HF, vitamin D supplementation may reduce disease progression and symptom severity through suppression of RAAS and PTH, down-regulation of inflammatory mediators, suppression of cardiac remodeling, promotion of cell growth and differentiation, reduction of blood pressure, and improvement in muscle strength.[14] However, studies have reported contradictory results, and some results were disappointing. Further large-scale randomized multicenter studies are needed to support role of routine vitamin D supplementation as part of clinical care for patients who underwent CHF.

Despite several studies demonstrating relationship between level of vitamin D and HF, exact mechanism by which vitamin D deficiency leads to poor clinical outcome has not been clearly established. Recently, growing evidence on pathophysiology of HF has shown that complex correlations between inflammatory cytokines, neurohormones, and vitamin D have an important role. Animal studies indicated that vitamin D inhibits RAAS, which then contributes to the salt and water retention seen in HF.[5] Overactivation of RAAS has also been reported in HF patients with vitamin D deficiency, and blockade of this system serves as cornerstone of medical management of HF.[6,13] In addition, vitamin D has a number of effects that should help prevent hypertension, an important risk factor for HF.[15]

Precise link between vitamin D deficiency and poor response to CRT is not yet known. Vitamin D plays important physiological role in controlling cardiac functions, and vitamin D-dependent signaling pathways are present in cardiac myocytes.[16] In animal studies, histological staining of cardiac tissue showed highly significant cellular hypertrophy and collagen deposition in vitamin D receptor knockout mice compared to wild-type mice. Vitamin D modulates myocardial extracellular matrix turnover acting on expression of both matrix metalloproteinases (MMPs), which hydrolyze extracellular matrix proteins, and tissue inhibitors of metalloproteinases (TIMPs). In vitamin D receptor knockout mice, unbalanced MMP/TIMP expression was associated with myocardial fibrosis and hypertrophy.[17] In addition, low levels of vitamin D have been shown to be inversely related to PRA. This results in increased level of aldosterone, which induces hypertrophy and dysregulation of proliferation and apoptosis in the myocardium and vessel wall. This in turn leads to fibrosis and chamber remodeling.[18] It was discovered that stimulation of collagen synthesis and deposition may account for negative response to CRT.[19] There was no decrease in collagen synthesis in non-responder patients. RAAS activation due to low level of vitamin D may prevent reverse remodeling effect of CRT. Low levels of vitamin D may contribute to the pro-inflammatory status in patients with HF, and may therefore play an important role in response to CRT.[13] Numerous reports have noted that CRT decreases inflammatory status of HF patients. In non-responder patients, markers related to inflammation do not decrease after CRT implantation. Low level of vitamin D may be associated with anti-inflammatory effect of CRT and decrease response to this therapy. Despite these possible explanations, it is unclear whether low levels of vitamin D are only a marker of response to CRT or an important factor to promote CRT response.

The main limitation of our study was small sample size, but this was the first study to evaluate role of vitamin D in CRT response. In addition, current guidelines include Class I recommendation for CRT in patients with QRS duration ≥150 ms. Only two-thirds of the patients in present study met this criterion. Finally, use of more rigorous methods than ELISA test will yield more accurate results.

Conclusion

In summary, to the best of our knowledge, this is the first study to show predictive value of vitamin D in CRT response. Although based upon limited number of patients, preimplantation vitamin D levels independently predicted CRT response. Therefore, assessment of vitamin D status appears useful before CRT implantation. The results of our study deserve further research. New studies that examine effect of vitamin D supplementation prior to implantation on CRT response with more patients would be useful.

Acknowledgements

This study was supported by a grant from the Turkish Society of Cardiology (No: 2010/1, Date: June 2, 2010). The authors would like to acknowledge and thank Hakan Çakır for his statistical advice during the revision phase of the current manuscript.

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: Cardiac resynchronization therapy; heart failure; vitamin D

Anahtar sözcükler: Kalp yetersizliği; kardiyak resenkronizasyon tedavisi; vitamin D.