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Original Article

Low vitamin D status associated with dilated cardiomyopathy

Veli Polat[1], Evin Bozcali[2], Turgut Uygun[1], Selçuk Opan[1], Osman Karakaya[1]

[1]*Department of Cardiology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey;*
[2]*Department of Cardiology, Koç University, School of Medicine, Istanbul, Turkey*

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Abstract: In recent years, a growing body of evidence supports that vitamin D plays a crucial role in various cardiovascular diseases. Cardiac muscle cells have vitamin D receptors as well as calcitriol-dependent Ca^{2+} binding protein. Therefore, the vitamin D may have an effect on cardiac function. In this research, we investigated the association between vitamin D status and dilated cardiomyopathy (DCMP). We compared serum 25-hydroxy-vitamin D3 (25OHD3) concentrations in 39 patients (mean age 50.4 ± 11.7 years, 15 women) with DCMP and in 35 healthy controls (mean age 54.6 ± 13.2 years, 17 women). Parathyroid hormone (PTH), calcium (Ca++), phosphorus, lipid profile, albumin and echocardiographic parameters (left-ventricular (LV) ejection fraction, LV fractional shortening, LV-end-diastolic and end-systolic dimensions) were measured in all study participants. The mean serum 25OHD3 concentrations in patients with the DCMP were significantly lower in compared to healthy controls (24.1 ± 10.4 ng/mL versus 41.4 ± 20.9 ng/mL, $P < 0.0001$). PTH concentrations were significantly higher in patients with DCMP in comparison with healthy controls (90.6 ± 29.8 pg/mL versus 49.1 ± 18 pg/mL, $P < 0.0001$). Additionally, we observed a significant negative correlation between 25OHD3 concentrations and PTH concentrations, LV end-diastolic dimensions, LV end-systolic dimensions (r = -0.66; $P < 0.0001$, r = -0.49; $P < 0.0001$, r = -0.50; $P < 0.0001$, respectively). Moreover, 25OHD3 was positively correlated with LV ejection fraction, LV fractional shortening, stroke volume, cardiac output, cardiac index (r = 0.46; $P < 0.001$, r = 0.44; $P < 0.001$, r = 0.25; $P = 0.03$, r = 0.37; $P < 0.001$, r = 0.25; $P = 0.03$; respectively). Our findings support that vitamin D has a potential role both in the development of DCMP and LV remodeling.

Keywords: Vitamin D, dilated cardiomyopathy, left ventricular remodeling

Introduction

The cases of vitamin D insufficiency are common both in the North American and in the European countries [1]. Vitamin D, a steroid hormone, is also well known for its necessary role in calcium balance and musculoskeletal metabolism. However, there is a growing body of evidence indicating that there may be a relationship between vitamin D deficiency and cardiovascular diseases [2, 3]. Vitamin D receptors present wide distribution throughout the cardiovascular system including vascular smooth muscle, endothelium, and cardiomyocytes [1, 2]. Recent studies reported that low vitamin D level is very common in the patients with heart failure and it is linked with poor prognosis among these patients [4, 5]. Chen and colleagues have also demonstrated that vitamin D-vitamin D receptor signaling system has a direct antihypertrophic effect on cardiomyocytes [6]. Additionally, previous studies indicate that there is a relationship between vitamin D and left ventricular geometry [7, 8].

Hypocalcemia due to vitamin D deficiency is an occasional and reversible cause of the DCMP, especially in the pediatric population. Calcium has an essential role in myocardial contraction and hypocalcemia that lead to congestive heart failure by reducing myocardial contractility. Hypocalcemic cardiomyopathy responds only to treatment with calcium and vitamin D [9, 10]. Zittermann et al. suggested that the low vitamin D level may play a role in the pathogenesis of the congestive heart failure. Cardiac muscle cells have vitamin D receptors as well as calcitriol-dependent Ca^{2+} binding protein [11]. Moreover, 1,25(OH)2-vitamin D3 stimulates the L-type voltage-dependent Ca^{2+} channels in the

Table 1. Baseline demographic, clinical, and biochemical data of the study population

Variable	DCMP Group (n = 39)	Control Group (n = 35)	*P* value
Age (years), mean (SD)	50.4 ± 11.7	54.6 ± 13.2	NS
Gender (Female/male)	15/24	17/18	NS
Diabetes mellitus, %	30.8	40	NS
Hypertension, %	35.9	42.9	NS
Smoking, %	33.3	22.9	NS
Postmenopausal women, %	53.3	51.4	NS
Systolic BP (mmHg), mean (SD)	123.6 ± 13.5	124 ± 15.7	NS
Diastolic BP (mmHg), mean (SD)	71.4 ± 6.8	71.7 ± 15.8	NS
BMI (kg/m^2), mean (SD)	23.6 ± 2.8	23.9 ± 2	NS
BSA (m^2), mean (SD)	1.7 ± 0.1	1.8 ± 0.1	NS
Fasting glucose (mg/dl), mean (SD)	103.3 ± 23.6	107.2 ± 32.7	NS
Total cholesterol (mg/dl), mean (SD)	185.9 ± 31.7	208.1 ± 33.4	0.004
hs-CRP (mg/L), mean (SD)	2.3 ± 1.1	1.3 ± 0.6	< 0.0001
Calcium (mg/dl), mean (SD)	8.3 ± 0.6	9.1 ± 0.3	< 0.0001
Phosphorus (mg/dl), mean (SD)	3.6 ± 0.3	3.2 ± 0.4	NS
Albumin (mg/dl), mean (SD)	4.0 ± 0.3	4.0 ± 0.4	NS
25OHD3 (ng/mL), mean (SD)	24.1 ± 10.4	41.4 ± 20.9	< 0.0001
PTH (pg/mL), mean (SD)	90.6 ± 29.8	49.1 ± 18	< 0.0001
ACE inhibitors/ARB, %	66.7	34.3	0.005
Beta blocker, %	51.3	31.4	NS
Adosterone antagonist, %	33.3	17. 1	NS

NS refers to non-significant; DCMP: dilated cardiomyopathy; BP: blood pressure; BMI: body mass index; BSA: body surface area; hs-CRP: high-sensitive C-reactive protein; 25OHD3: 25-hydroxy-vitamin D3; PTH: parathyroid hormone; ACEI: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker. Values are express as mean ± SD or otherwise identified.

cardiac muscle cells through guanine nucleotide binding protein-mediated stimulation of the adenylate cyclase/cAMP/protein kinase A messenger system [12]. Therefore, vitamin D may have an effect on cardiac function, and vitamin D deficiency may play a role in the pathogenesis of the DCMP.

In this trial, we intended to investigate an association between vitamin D status and the DCMP. Additionally, we examined the relationship between serum 25OHD3 concentrations and the LV dimensions and function in patients with DCMP.

Materials and methods

Study population

We enrolled 39 consecutive patients (mean age 50.4 ± 11.7 years, 15 women) with the diagnosis of the DCMP according to the World Health Organization criteria [13] from the Cardiology Department of Bakirkoy Dr. Sadi Konuk Education and Research Hospital between August 2011-February 2014. The 35 healthy participants (mean age 54.6 ± 13.2 years, 17 women) were enrolled the study as a control group. All study participants underwent physical examinations, blood analysis, and echocardiographic evaluation.

We did not enroll the patients with primary hyperparathyroidism, hypercalcaemia, osteoporosis, chronic renal insufficiency (estimated creatinine clearance < 30 ml/min), chronic liver disease, malignancy, coronary artery disease, nephrolithiasis, drug and alcohol addiction, under estrogen, androgen, parathyroid hormone, corticosteroid, and vitamin D therapy, systemic inflammatory diseases.

The local Ethics Committee approved the study and written informed consent was obtained from all participants. The study was performed apropos the principles of the Declaration of Helsinki.

Laboratory analysis

Venous blood samples were collected in the morning after an overnight fast (10 to 12 hours). Afterwards, the serum was separated via centrifugation and immediately transported to the laboratory for biochemical analysis. Serum total cholesterol, hs-CRP, glucose, phosphorus, calcium and albumin concentrations were measured by standard laboratory methods. The serum concentration of 25OHD3 was measured by radioimmunoassay on the Architect i2000 (Abbott Laboratories). The serum PTH concentration was assessed by immunoassay method (Siemens Immulite, Siemens Healthcare Diagnostics, Deerfield, IL).

Table 2. Baseline echocardiographic data of the study participants

Variable	DCMP Group (n = 39)	Control Group (n = 35)	*P* value
LVEF (%)	27.6 ± 5.7	61.4 ± 5.6	< 0.0001
LVFS (%)	13.1 ± 2.9	33 ± 4	< 0.0001
Stroke Volume (ml)	48.4 ± 7.8	65.1 ± 17.7	< 0.0001
LVEDD (mm)	71.1 ± 7.9	46.2 ± 6.8	< 0.0001
LVESD (mm)	61.6 ± 8.3	30.8 ± 5.2	< 0.0001
CI (L/min/m^2)	1.9 ± 0.5	2.7 ± 0.7	< 0.0001
CO (L/min)	3.2 ± 0.8	4.4 ± 1.1	< 0.0001

DCMP refers to dilated cardiomyopathy; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; CI: cardiac index; CO: cardiac output.

Echocardiographic evaluation

All study population underwent transthoracic Doppler echocardiographic examination (Vivid S5 Cardiovascular Ultrasound Systems, GE Healthcare, WI, U S A) and they were connected to an electrocardiogram monitor for recording their heart rate throughout the echocardiographic examination. The same cardiologist, who was blinded to the patient data, established complete echocardiographic evaluation of the patients. Standard apical four-chamber, parasternal short and long axis views of the LV were taken to determine echocardiographic parameters. The aortic annulus, LV end-diastolic and LV end-systolic diameters were assessed in the parasternal long axis view, using 2-dimensional guided M-mode echocardiography in accordance with the recommendations of the chamber quantification [14].

The maximum instantaneous aortic flow velocity was measured in the ascending aorta with continuous wave Doppler directed from the suprasternal window, when the patients were in supine position. The time-velocity integral values of 10 consecutive cardiac cycles were averaged to calculate the mean time-velocity integral. The time-velocity integral values were calculated during the held expiration. Stroke volume (SV) was calculated from the product of the mean time-velocity integral and the cross-sectional area of the aortic annulus orifice. Cardiac output (CO) was estimated from the product of SV and heart rate [15]. Cardiac index (CI) was determined as cardiac output divided by the body surface area. Left ventricular fractional shortening (LVFS) was computed in all study subjects. The left ventricular ejection fraction (LVEF) was assessed by the Simpson's method. Endocardial borders of the left ventricle were traced from apical four-chamber view during end-diastole and end-systole. Then, the software automatically estimated the LVEF [14].

Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation (SD) for continuous variables and proportion (%) or frequency for categorical variables. The Kolmogorow-Smirnov test was used to determine the normality of distribution of the variables. The independent samples t-test and the Mann-Whitney U test were used to compare continuous variables. The chi-squared test was used to analyze categorical data. Correlations between the variables were assessed by the Spearman and the Pearson coefficient analyses. A *P* value < 0.05 was considered as statistically significant. All statistical analyses were carried out with the Statistical Package for Social Science for Windows version 21.0 (SPSS Inc., Chicago, IL).

Results

The baseline demographic, clinical, and biochemical data including serum 25OHD3 and PTH concentrations of the study population are shown in **Table 1**. Additionally, **Table 2** shows the baseline echocardiographic data of the study participants. The mean serum 25OHD3 concentrations in patients with the DCMP were significantly lower in compared to healthy controls (24.1 ± 10.4 ng/mL versus 41.4 ± 20.9 ng/mL, *P* < 0.0001). PTH concentrations were significantly higher in patients with DCMP in comparison with healthy controls (90.6 ± 29.8 pg/mL versus 49.1 ± 18 pg/mL, *P* < 0.0001). Age, gender, smoking, hypertension, diabetes mellitus, systolic and diastolic blood pressures, BMI, BSA, mean serum fasting glucose, phosphorus and albumin concentrations were similar in both groups. Study groups were comparable in terms of medication usage, except for ACE inhibitors/ARB, which the use of ACE inhibitors/ARB was more frequent in the DCMP group. Additionally, mean serum total cholesterol and calcium concentrations were significantly lower in patients with DCMP than in the

Table 3. Correlation between serum 25OHD3 concentrations and echocardiographic parameters

Parameter	*Correlation coefficient (r)*	*P*
LVEF	0.46	< 0.0001
LVFS	0.44	< 0.0001
LVEDD	-0.49	< 0.0001
LVESD	-0.50	< 0.0001
SV	0.25	0.03
CO	0.37	0.001
CI	0.25	0.03

LVEF refers to left ventricular ejection fraction; LVFS: left ventricular fractional shortening; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; SV: stroke volume; CO: cardiac output; CI: cardiac index.

healthy controls. While mean hs-CRP concentration was significantly higher in patients with DCMP compared to control group (**Table 1**).

Stroke volume, cardiac output, cardiac index, LV fractional shortening, LVEF were significantly lower; otherwise left ventricular end-diastolic and end-systolic diameters were significantly higher in patients with DCMP compared to the healthy controls (**Table 2**). There was a significantly negative correlation between 25OHD3 concentrations and PTH concentrations, LV end-diastolic dimensions, LV end-systolic dimensions (r = -0.66; $P < 0.001$, r = -0.49; $P < 0.001$, r = -0.50; $P < 0.001$, respectively; **Table 3**). Moreover, 25OHD3 was positively correlated with LVEF, LVFS, SV, CO, CI (r = 0.46; $P < 0.001$, r = 0.44; $P < 0.001$, r = 0.25; $P = 0.03$, r = 0.37; $P < 0.001$, r = 0.25; $P = 0.03$ respectively; **Table 3**).

Discussion

In this study, we observed significantly lower concentrations of 25OHD3 among patients with DCMP as compared to healthy controls. Moreover, according to the mean concentrations of 25OHD3, vitamin D status of patients with DCMP was insufficient according to the current guidelines (the recommended threshold for sufficiency is ≥ 30 ng per milliliter) [16]. Vitamin D exerts direct and indirect effects on the cardiovascular (CV) system. Direct effects of vitamin D on the myocardium can be listed as anti-hypertrophic effects on cardiomyocytes via diminishing the expression of relevant genes [17, 18], inhibition of the cardiac renin-angiotensin system [19, 20], regulation of the myocardial extracellular matrix turnover [21], nongenomic and genomic actions on the cardiac contractility and intracellular calcium handling, regulation of myosin expression and regulation of heart energy metabolism [22]. Vitamin D also indirectly prevents myocardium with its antihypertensive, anti-atherosclerotic, anti-diabetic, anti-autoimmunological properties and its effect on immune system that increasing resistance against the infectious disease [22]. A deficiency of vitamin D can also stimulate PTH secretion in response to hypocalcemia. According to recent reports, elevated PTH levels are associated with increased CV risk factors, CV diseases, as well as CV mortality. Furthermore, this deleterious impact of the PTH on the CV system still persists after the adjustment for 25OHD3, renal function and standard risk factors [23, 24]. Therefore, another indirect preventive effect of vitamin D on myocardium is preclusion of excessive secretion of the PTH. Coherently, we found that DCMP patients had significantly higher serum PTH concentrations compared to controls and we observed a significant inverse relationship between 25OHD3 and PTH concentrations. More recently, it was reported that increased PTH level was independently associated with subclinical LV systolic dysfunction in patients with severe psoriasis [25]. Additionally, Wannamethee et al. just reported that elevated PTH, but not 25OHD3 or other biomarkers of mineral metabolism, is related with increased risk of incident heart failure in older men with and without CV disease [26]. In the light of these findings, PTH may contribute independently to myocardial dysfunction in patients with DCMP.

DCMP is the third most common cause of heart failure with a wide range of etiologies such as genetic, infectious, autoimmune, toxic, metabolic, nutritional, endocrine, mitrochondrial. However, in some cases the exact etiology remains unclear [27]. Hypocalcaemia is one of the infrequent and reversible causes of the DCMP. Some case reports indicated that the DCMP can be associated with hypocalcaemia and vitamin D deficiency in the pediatric population. Mostly, these cases were successfully treated with calcium and vitamin D replacement therapy, then cardiac dysfunction and dilatation completely resolve within months [9, 28, 29]. Conversely, hypocalcaemic DCMP is generally due to hypoparathyroidism rather

than vitamin D deficiency in the adult population [30, 31]. However, hypocalcaemic cardiac dysfunction secondary to severe vitamin D deficiency in adults has been reported in only a few cases to date [32, 33]. Calcium directly affects the strength of myocardial contraction via excitation-contraction coupling. Low calcium levels decrease the myocardial contractility and lead to hypocalcaemic cardiomyopathy, which is usually unresponsive to conventional therapy for heart failure, only improves with the restoration of normal calcium levels [10]. In our study, serum calcium concentrations were significantly lower in patients with DCMP. Exclusively, lower serum calcium concentrations could be a reason for myocardial dysfunction in patients with DCMP. Nevertheless, we observed significantly lower 25OHD3 concentrations accompanied by elevated PTH concentrations in the DCMP patients, which indicates that vitamin D deficiency underlies the hypocalcaemia. Thus, hypocalcaemia is another indirect deleterious effect of vitamin D deficiency on cardiac function.

Our results are not sufficient to prove a causal relationship between vitamin D deficiency and DCMP. It is uncertain whether vitamin D deficiency is a cause or consequence of the heart failure in patients with DCMP. Lack of sunlight exposure due to limited functional capacity and avoiding outdoor activities especially during the summer time may also contribute to low 25OHD3 concentrations in patients with DCMP [7, 34]. Also, reduced dietary vitamin D intake and absorption are other possible causes of low vitamin D status in patients with DCMP [35].

To our knowledge, the present study demonstrates for the first time that there is an inverse relationship between 25OHD3 and LV dimensions in adult DCMP patients. Previously, Ameri et al. reported that 25OHD3 was negatively correlated with LVESD and LV volume in patients with heart failure [36]. Ameri et al. indicated a significant nonlinear relation between 25OHD3 and LV concentric remodelling in community-dwelling subjects without heart disease [7]. Moreover, higher circulating vitamin D concentrations were associated with favorable LV geometry and LV systolic function among older adults without cardiovascular disease [7, 8]. Taken together with our current findings, we can suggest that vitamin D may play a key role in the LV remodeling. We also found a positive association between 25OHD3 and LVEF, LV fractional shortening, stroke volume, cardiac output, and cardiac index in the DCMP patients.

It has been shown that treatment with calcitriol, an active form of vitamin D, regresses cardiac hypertrophy in patients on hemodialysis [37]. More recent clinical studies have demonstrated that vitamin D supplementation improves survival and the NYHA functional class, and it also lowers serum pro-brain natriuretic peptide, plasma renin activity and plasma renin concentration in vitamin D-deficient heart failure patients [20, 34, 38]. Recently, Dalbeni et al reported that vitamin D supplementation for 6 months achieves a substantial improvement in the EF values of elderly patients with heart failure and vitamin D deficiency [39]. Severe vitamin D deficiency can be the underlying cause of some DCMP cases in which supplementation therapy completely reverses cardiac dysfunction and dilatation. Therefore, vitamin D deficiency must be considered as an underlying reason of myocardial dysfunction in patients with DCMP because it is one of the rare reversible causes of the DCMP. The exact prevalence of vitamin D deficiency-induced DCMP, however, is unknown especially in the adult population. Future larger community-based studies are needed to elucidate the frequency of vitamin D deficiency-induced DCMP.

Several potential limitations are present in our study. Firstly, the sample size of the present study is small to generalize to all patients with DCMP. Secondly, current study is an observational study and it fails to prove a causal relationship between vitamin D deficiency and the DCMP. It also fails to determine precise role of vitamin D in the pathogenesis of DCMP. Thirdly, only one measurement of 25OHD3 may be limited to reveal the exact long-standing status of the vitamin D in patients with DCMP.

In conclusion, in this study we suggest that vitamin D deficiency is more common in patients with DCMP than it has been previously supposed. Although the current study does not establish the exact causal relationship between vitamin D deficiency and DCMP, vitamin D deficiency-induced DCMP should not be disregarded in adult patients. According to our findings, we strongly recommend vitamin D screening especially in adult patients with DCMP. DCMP

patients, who have vitamin D deficiency, should be promptly treated with vitamin D supplementation and patients should be monitored for the restoration of cardiac function and dimensions. Future investigations are needed to shed light on the possible causal linkage between vitamin D and DCMP and the precise role of vitamin D in the pathogenesis of the DCMP and/or heart failure. Lastly, further larger randomized placebo-controlled trials are also required to assess the effectiveness of vitamin D supplementation therapy in patients with DCMP who are vitamin D deficient.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Evin Bozcali, Department of Cardiology, Koç University, School of Medicine, Istanbul, Turkey. E-mail: epolat@kuh.ku.edu.tr

References

[1] Holick MF. High prevelance of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81: 353-373.

[2] Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117: 503-511.

[3] Judd SE, Tangpricha V. Vitamin D. deficiency and risk for cardiovascular disease. Am J Med Sci 2009; 338: 40-44.

[4] Liu LC, Voors AA, van Veldhuisen DJ, van der Veer, Belonje AM, Szymanski MK, Sillje HH, van Gilst WH, Jaarsma T, de Boer RA. Vitamin D status and outcomes in heart failure patients. Eur J Heart Fail 2011; 13: 619-625.

[5] Schierbeck LL, Jensen TS, Bang U, Jensen G, Kober L, Jensen JE. Parathyroid hormone and vitamin D-markers for cardiovascular and all cause mortality in heart failure. Eur J Heart Fail 2011; 13: 626-632.

[6] Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, Zhang Y, Yeghiazarians Y, Gardner DG. Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. Circulation 2011; 124: 1838-1847.

[7] Ameri P, Canepa M, Milaneschi Y, Spallarossa P, Leoncini G, Giallauria F, Strait JB, Lakatta EG, Brunelli C, Murialdo G, Ferrucci L. Relationship between vitamin D status and left ventricular geometry in a healthy population: results from the Baltimore Longitudinal Study of Aging. J Intern Med 2013; 273: 253-262.

[8] Fall T, Shiue I, Bergeå af Geijerstam P, Sundström J, Ärnlöv J, Larsson A, Melhus H, Lind L, Ingelsson E. Relations of circulating vitamin D concentrations with left ventricular geometry and function. Eur J Heart Fail 2012; 14: 985-991.

[9] Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, Archer N, Mok Q, Daubeney P, Tulloh R, Burch M. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart 2008; 94: 581-584.

[10] Sanyal D, Raychaudhuri M. Infants with dilated cardiomyopathy and hypocalcemia. Indian J Endocrinol Metab 2013; 17: S221-S223.

[11] Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 2003; 41: 105-112.

[12] De Boland AR, Boland RL. Non-genomic signal transduction pathway of vitamin D in muscle. Cell Signal 1994; 6: 717-724.

[13] Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 1996; 93: 841-842.

[14] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD Spencer KT, Sutton MSJ, Stewart WJ. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiography 2005; 18: 1440-1463.

[15] Hara K, Floras JS. Effects of naloxone on hemodynamics and sympathetic activity after exercise. J Appl Physiol 1993; 73: 2028-2035.

[16] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.

[17] Nibbelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU. 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. J Steroid Biochem Mol Biol 2007; 103: 533-537.

[18] Chen S, Glenn DJ, Ni W, Grigsby CL, Olsen K, Nishimoto M, Law CS, Gardner DG. Expression of the vitamin D receptor is increased in the hypertrophic heart. Hypertension 2008; 52: 1106-1112.
[19] Pörsti IH. Expanding targets of vitamin D receptor activation: downregulation of several RAS components in the kidney. Kidney Int 2008; 74: 1371-1373.
[20] Schroten NF, Ruifrok WP, Kleijn L, Dokter MM, Silljé HH, Heerspink HJ, Bakker SJ, Kema IP, van Gilst WH, van Veldhuisen DJ, Hillege HL, de Boer RA. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: An open-label, blinded end point, randomized prospective trial (VitD-CHF trial). Am Heart J 2013; 166: 357-364.
[21] Weber KT, Weglicki WB, Simpson RU. Macro- and micronutrient dyshomeostasis in the adverse structural remodeling of myocardium. Cardiovasc Res 2009; 81: 500-508.
[22] Pilz S, Tomaschitz A, Drechsler C, Dekker JM, Marz W. Vitamin D deficiency and myocardial diseases. Mol Nutr Food Res 2010; 54: 1103-1113.
[23] Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. Curr Osteoporos Rep 2008; 6: 77-83.
[24] Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappe DL, Muhlestein JB. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: Dependent or independent risk factors? Am Heart J 2011; 162: 331-339. e2.
[25] Zhao CT, Yeung CK, Siu CW, Tam S, Chan J, Chen Y, Chan HH, Tse HF, Yiu KH. Relationship between parathyroid hormone and subclinical myocardial dysfunction in patients with severe psoriasis. J Eur Acad Dermatol Venereol 2014; 28: 461-468.
[26] Wannamethee SG, Welsh P, Papacosta O, Lennon L, Whincup PH, Sattar N. Elevated parathyroid hormone, but not vitamin D deficiency, is associated with increased risk of heart failure in older men with and without cardiovascular disease. Circ Heart Fail 2014; 7: 732-9.
[27] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006; 113: 1807-1816.
[28] Brown J, Nunez S, Russell M, Spurney C. Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature. Pediatr Cardiol 2009; 30: 818-823.
[29] Carlton-Conway D, Tulloh R, Wood L, Kanabar D. Vitamin D deficiency and cardiac failure in infancy. J R Soc Med 2004; 97: 106-108.
[30] Bansal B, Bansal M, Bajpai P, Garewal HK. Hypocalcemic cardiomyopathy-different mechanisms in adult and pediatric cases. J Clin Endocrinol Metab 2014; 99: 2627-32.
[31] Jung YJ, Kim SE, Hong JY, Lee JH, Park DG, Han KR, Oh DJ. Reversible dilated cardiomyopathy caused by idiopathic hyoparathyroidism. Korean J Intern Med 2013; 28: 605-608.
[32] Grecian S, Ainslie M, Liliker J, Sarma J. Decompensated heart failure secondary to hypocalcemia post coronary artery bypass grafting. BMJ Case Rep 2011.
[33] Lee P, Milliken S, Center JR. Hypocalcaemic cardiac failure post BMT secondary to unrecognized vitamin D deficiency. Bone Marrow Transplant 2008; 42: 363-364.
[34] Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, Admon D. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012; 14: 357-366.
[35] Hughes CM, Woodside JV, McGartland C, Roberts MJ, Nicholls DP, McKeown PP. Nutritional intake and oxidative stress in chronic heart failure. Nutr Metab Cardiovasc Dis 2012; 22: 376-382.
[36] Ameri P, Ronco D, Casu M, Denegri A, Bovio M, Menoni S, Ferone D, Murialdo G. 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.
[37] Kim HW, Park CW, Shin YS, Kim YS, Shin SJ, Kim YS, Choi EJ, Chang YS, Bang BK. Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. Nephron Clin Pract 2006; 102: c21-c29.
[38] Amin A, Minaee S, Chitsazan M, Naderi N, Taghavi S, Ardeshiri M. Can vitamin D supplementation improve the severity of congestive heart failure? Congest Heart Fail 2013; 19: E22-E28.
[39] Dalbeni A, Scaturro G, Degan M, Minuz P, Delva P. Effects of six months of vitamin D supplementation in patients with heart failure: A randomized double-blind controlled trial. Nutr Metab Cardiovasc Dis 2014; 24: 861-868.