

Study of Vitamin D status in patients with dilated cardiomyopathy at a teaching hospital in North India

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Abstract

Background: Vitamin D plays a vital role in maintaining adequate serum calcium and phosphate levels for bone mineralization and optimal skeletal health. Recent literature, however, have indicated a much broader role of vitamin D than simply the regulation of calcium metabolism as vitamin D receptors (VDRs) are found in a variety of cells and tissue. **Aim:** Aim of our work was to evaluate presence of hypovitaminosis D in patients with dilated cardiomyopathy and to study any correlation of echocardiographic parameters with vitamin D deficiency. **Material and method:** An observational cross-sectional hospital based study, 26 patients diagnosed to have dilated cardiomyopathy and 26 age, gender and body mass index matched controls who were patients of other medical illnesses were included into the study between January- 2012 to December 2014 at Era's Lucknow Medical College and Hospital, Lucknow according to World Health Organization criteria. **Results:** There were no differences in age gender, body mass index and sun exposure within the groups. Prevalence of diabetes mellitus and hypertension was similar in the two groups. Biochemical parameters were not significantly different in all study participants except that patients with DCMP had low calcium levels than the control group. **Conclusion:** Patients with DCMP had lower vitamin D levels than controls and vitamin D deficiency had significant correlation with cardiac function. Therefore, screening for vitamin D deficiency along with prompt treatment is recommended in patients with DCMP. Future studies are needed to address the precise role of vitamin D deficiency in causation of DCMP.

Keywords: *vitamin D, cardiomyopathy.*

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Received Date: 15/02/2016 Revised Date: 11/03/2016 Accepted Date: 02/04/2016

Access this article online

Quick Response Code:	Website: www.medpulse.in
	DOI: 04 April 2016

INTRODUCTION

Vitamin D plays a vital role in maintaining adequate serum calcium and phosphate levels for bone mineralization and optimal skeletal health. Recent literature, however, have indicated a much broader role of vitamin D than simply the regulation of calcium metabolism as vitamin D receptors (VDRs) are found in a variety of cells and tissues. These include malignant breast, colon, and prostate cells and normal cells of the

immune system, kidney, heart, and vasculature. Vitamin D likely confers physiologically relevant pleiotropic functions that include cardioprotective and immunomodulatory effects as well as enhances antimicrobial function and its deficiency could lead to increased risk of cardiovascular disease and cancer.^{1, 2} The heart is particularly noteworthy in that plasma 25(OH) vitamin D3 [25(OH)D3] levels have been shown to correlate inversely with the incidence of a variety of cardiac disorders including ischemic heart disease and heart failure.^{3, 4} Role of vitamin D in myocardial contractility was demonstrated in a community study of 870 elderly patients without heart disease during which higher circulating vitamin D levels were found to correlate with better left ventricular (LV) systolic function and smaller LV end-systolic diameter.⁵ 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, mitochondrial in origin. However, in some cases the exact etiology remains unclear.⁶ B-type natriuretic

peptide (BNP) is a hormone released by ventricular cardiomyocytes in response to increased myocardial stretch and volume overload and can be considered quantitative markers of hemodynamic cardiac stress. BNP and N terminal pro BNP activation have been shown to be a diagnostic marker and predictor of poor outcome and in patients with heart failure.^[7] Aim of our work was to evaluate presence of hypovitaminosis D in patients with dilated cardiomyopathy and to study any correlation of echocardiographic parameters with vitamin D deficiency.

MATERIAL AND METHODS

In an observational cross-sectional hospital based study, 26 patients diagnosed to have dilated cardiomyopathy and 26 age, gender and body mass index matched controls who were patients of other medical illnesses were included into the study between January-2012 to December 2014 at Era's Lucknow Medical College and Hospital, Lucknow according to World Health Organization criteria.⁸

Exclusion criteria included concurrent cytotoxic chemotherapy, pregnancy or lactation, sarcoidosis, hyperparathyroidism, current or recent (<1 year) use of

vitamin D and/or calcium supplements, and patients on anticonvulsants thiazide or any other drug interfering with vitamin D. Patients with chronic liver disease, renal disease, gastric or bowel resection, malabsorption states such as chronic pancreatitis and inflammatory bowel diseases were also excluded.

All study participants underwent physical examinations, blood analysis, and echocardiographic evaluation. The Local Ethics Committee approved the study and written informed consent was obtained from all study participants.

Statistical Analysis

The SPSS 13.0 (SPSS Inc., Chicago, Ill) statistical software package was used for statistical analyses. Results are presented as mean±SD or as percentages and numbers for categorical data. Normality tests were used for all variables. Continuous variables that were normally distributed were analyzed with using t-test for Independent samples, and unequally distributed variables were analyzed with Mann-Whitney U test. Correlations between 25 (OH) D and other variables were determined by Spearman correlation test.

RESULTS

Table 1: Baseline characteristics of patients and controls

Variables	Patients with DCMP(n=26)	Controls(n=26)
Age(Years)	52 ±5.6	50 ±3.8
Male:Female	14/12	13/13
Body Mass Index(kg/m2)	22.8 ±1.6	23.2 ±1.8
Hypertension(%)	6(23)	7(27)
Diabetes Mellitus(%)	9(35)	8(31)

Table 2: Biochemical parameters of patients with dilated cardiomyopathy and controls

Variables	Patients with DCMP(n=26)	Controls(n=26)	P value
Fasting plasma glucose (mg/dl)	100± 24.2	104± 18.6	0.12
Total Cholesterol(mg/dl)	180 ±26.6	172± 30.8	0.07
LDL(mg/dl)	90± 12	82±17	0.05
Hemoglobin(mg/dl)	10.6± 1.8	11.2± 2.8	0.04
Creatinine(mg/dl)	0.9± 0.06	0.84 ±0.04	0.08
Albumin(mg/dl)	3.6± 1.2	4.0 ±1.4	0.05
Calcium(mg/dl)	8.2± 1.2	9.4± 0.2	0.02
25OHD3(ng/ml)	18.4± 8.6	30± 12.4	0.001
Parathyroid hormone(pg/ml)	94.5± 26.6	48 ±17.2	0.01
NT proBNP(pg/ml)	3482± 1256	165± 34	0.001

Table 3: Correlations with hypovitaminosis D

Parameter	Correlation coefficient	P value
LVEF	0.38	0.001
LVFS	0.40	0.001
LVEDD	0.39	0.01
LVESD	0.42	0.001
NT proBNP	0.40	0.002

LVEF: Left ventricle ejection fraction; **LVFS:** Left ventricle fractional shortening; **LVEDD:** Left ventricle end diastolic diameter; **LVESD:** Left ventricle end systolic diameter

The baseline characteristics of the two groups are shown in Table 1. There were no differences in age, gender, body mass index and sun exposure within the groups. Prevalence of diabetes mellitus and hypertension was similar in the two groups. Biochemical parameters were not significantly different in all study participants except that patients with DCMP had low calcium levels than the control group.

Table 2 shows mean 25 OHD3 levels were significantly lower (18.4 ± 8.6 ng/ml vs 30 ± 12.4 ng/ml, $p=0.002$) while parathyroid hormone (94.5 ± 26.6 pg/ml vs 48 ± 17.2 pg/ml, $p=0.01$) and NT pro BNP levels were significantly greater in patients with DCMP than controls.

In DCMP group 12/26 patients had severe vitamin D deficiency while in control group 6/26 patients had severe hypovitaminosis D.

As far as echocardiographic parameters were concerned, LV fractional shortening and ejection fraction (LVEF) were significantly lower in patients with DCMP and left ventricular end-diastolic and end-systolic diameters were significantly higher in patients with DCMP compared to the controls. There was a significant negative correlation between 25OHD3 concentrations and LV end-diastolic dimensions and LV end-systolic dimensions ($r = -0.39$; $P = 0.01$, $r = -0.42$; $P = 0.001$, respectively as shown in Table 3 and serum NT pro BNP levels ($r = -0.40$; $P = 0.002$). On the contrary 25OHD3 levels were positively correlated with LVEF and LVFS ($r = 0.38$; $P = 0.001$, $r = 0.40$; $P = 0.001$ respectively).

DISCUSSION

Several studies from different parts of our country have pointed towards widespread vitamin D deficiency in Indians of all age groups residing in rural or urban areas. [11],[12] Skin complexion, poor sun exposure, vegetarian food habits and lack of vitamin D food fortification programme in the country explain the high prevalence of VDD in India despite its sunny climate. We also conducted a study to assess the vitamin D status patients with pulmonary tuberculosis who were sputum positive. [13] In the present study, it was observed that 25 OHD3 levels were lower than normal in both the groups and very significantly low in patients with dilated cardiomyopathy than controls who were also the patients with other medical illnesses. There was a negative correlation between 25OHD3 and LV dimensions in DCMP patients. This observation was in concordance with Ameri *et al* who also reported that 25OHD3 level had inverse relation with LVESD and LV volume in patients with heart failure. [14] Calcium directly affects the strength of myocardial contraction via excitation-contraction coupling. Hypocalcaemia due to vitamin D deficiency have been incriminated as reversible cause of

cardiomyopathy in pediatric population [15, 16] while hypocalcaemic DCMP was reported due to hypoparathyroidism in the adult population. [17, 18] Vitamin D exerts multiple effects on the cardiovascular system including anti-hypertrophic effects on cardiomyocytes via diminishing the expression of relevant genes. [19] Cardiomyocytes possess vitamin D receptors as well as calcitriol-dependent Ca^{2+} binding protein. Therefore, vitamin D deficiency may play a role in the pathogenesis of the DCMP. [20] Several studies have shown associations of low vitamin D concentrations with cardiovascular events including sudden cardiac death and mortality with heart failure patients. [21-24] In a study drawn from the NHANES III database, vitamin D insufficiency was associated with heart failure. [25] In another study of patients vitamin D levels were negatively correlated with N-terminal pro-BNP, a marker of cardiac dysfunction and failure, and negatively correlated with NYHA classification and impaired LV function. After correction for cardiovascular risk factors, the hazard ratio for death due to heart failure was significantly higher when vitamin D deficient patients with 25(OH)D levels <10 ng/ml were compared with replete patients with levels >30 ng/ml. [22] Interestingly, a recent report linked a functional polymorphism in the 1-(OH)ase gene, the rate-limiting step in the synthesis of active 1,25(OH)₂ with increased risk for heart failure. [26] Lack of vitamin D could cause diastolic dysfunction and the Hoorn study found a trend towards increased risk of diastolic dysfunction in persons with vitamin D deficiency, considering 614 persons from a population-based cohort of older men and women. [27] Vitamin D deficiency causes hypocalcemia and secondary hyperparathyroidism. In our study, DCMP patients had significantly higher serum PTH concentrations compared to controls and there was a significant inverse relationship between 25OHD3 and PTH concentrations. Similar observations were reported by Laguardia *et al* in another study, [28] where serum parathormone (PTH) was elevated in patients with congestive heart failure due to ischemic or dilated cardiomyopathy and hypovitaminosis D was present in them. Wannamethee *et al.* demonstrated in their study that elevated PTH was related with increased risk of incident heart failure in older men with and without CV disease. [29]

A meta-analysis concluded that PTH might contribute independently to myocardial dysfunction in patients with DCMP. [30] The majority of congestive heart failure patients have insufficient vitamin D, due to reduced sunlight exposure, difficult mobilization and outdoor activity, nutritional factors, and malabsorption of vitamin D due to intestinal edema in severe right heart failure and comorbidities, such as obesity and renal and hepatic

failure. Our study has got several limitations. Being a cross sectional one, neither we could prove causal relationship between vitamin D deficiency and the DCMP nor we could demonstrate exact role of vitamin D in pathogenesis of heart failure. In view of small sample size of our study we would suggest a prospective study having large number of patients with long follow up to determine the precise role of vitamin D in the pathogenesis of DCMP.

CONCLUSION

Patients with DCMP had lower vitamin D levels than controls and vitamin D deficiency had significant correlation with cardiac function. Therefore, screening for vitamin D deficiency along with prompt treatment is recommended in patients with DCMP. Future studies are needed to address the precise role of vitamin D deficiency in causation of DCMP.

REFERENCES

1. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, *et al.* Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. *Autoimmun Rev.* 2010;9:709–15.
2. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, *et al.* Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med.* 2008;168:1340–9.
3. Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, *et al.* 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: 357–66.
4. Karakas M, Thorand B, Zierer A, Huth C, Meisinger C, Roden M, *et al.* Low levels of serum 25-hydroxyvitamin D are associated with increased risk of myocardial infarction, especially in women: results from the MONICA/KORA Augsburg case-cohort study. *J Clin Endocrinol Metab* 2013; 98: 272–80.
5. Fall T, Shiue I, Bergea af Geijerstam P, Sundstrom J, Arnlöv J, Larsson A *et al.* Relations of circulating vitamin D concentrations with left ventricular geometry and function. *Eur J Heart Fail.* 2012;14:985–91.
6. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D *et al.* 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: 1807-16.
7. Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, *et al.* Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. *Eur Heart J* 2012;33:2001–6.
8. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O’Connell J, *et al.* 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: 841-2.
9. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358–67.
10. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;6:266–81.
11. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. *Am J Clin Nutr* 2000; 72 : 472-5.
12. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, *et al.* High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians. *Am J Clin Nutr* 2007; 85:1062-7.
13. Karoli R, Fatima J, Gupta SS, Shukla V, Moidurrehman, Manhar M. Vitamin D Deficiency in Medical Patients at a Teaching Hospital in North India. *J Assoc Physicians India.* 2015;63:35-8.
14. Ameri P, Ronco D, Casu M, Denegri A, Bovio M, Menoni S, *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;20:633–40.
15. Cox GF, Sleeper LA, Lowe AM, Towbin JA, Colan SD, Orav EJ, *et al.* Factors associated with establishing a causal diagnosis for children with cardiomyopathy. *Pediatrics* 2006;118:1519-31.
16. Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, *et al.* Hypocalcaemia and vitamin D deficiency: An important, but preventable, cause of life-threatening infant heart failure. *Heart* 2008;94:581-4.
17. Jung YJ, Kim SE, Hong JY, Lee JH, Park DG, Han KR, Oh DJ. Reversible dilated cardiomyopathy caused by idiopathic hypoparathyroidism. *Korean J Intern Med.* 2013;28:605–8.
18. Csanády M, Forster T, Julesz J. Reversible impairment of myocardial function in hypoparathyroidism causing hypocalcaemia. *Br Heart J* 1990;63:58-60.
19. 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;52:1106–12
20. 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;41:105–12.
21. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008; 168:1340–9.
 22. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP *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: 3927–35.
 23. Cozzolino M, Ketteler M, Zehnder D. The vitamin D system: a crosstalk between the heart and kidney. *Eur J Heart Fail* 2010; 12: 1031-41.
 24. Pilz S, Tomaschitz A, Drechsler C, Dekker JM, Marz W. Vitamin D deficiency and myocardial diseases. *Mol Nutr Food Res* 2010; 54:1103-13.
 25. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008;102:1540–4.
 26. Wilke RA, Simpson RU, Mukesh BN, Bhupathi SV, Dart RA, Ghebranious NR *et al.* Genetic variation in CYP27B1 is associated with congestive heart failure in patients with hypertension. *Pharmacogenomics* 2009; 10: 1789–97.
 27. Pilz S, Henry RM, Snijder MB, van Dam RM, Nijpels G, Stehouwer CD, *et al.*, Vitamin D deficiency and myocardial structure and function in older men and women: the Hoorn study. *J Endocrinol Invest.* 2010;33:612-6177.
 28. Laguardia SP, Dockery BK, Bhattacharya SK, Nelson MD, Carbone LD, Weber KT. Secondary hyperparathyroidism and hypovitaminosis D in African-Americans with decompensated heart failure. *The American Journal of the Medical Sciences* 2006;332: 112–8.
 29. 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.
 30. van Ballegooijen AJ, Reinders I, Visser M, Brouwer IA. . Parathyroid hormone and cardiovascular disease events: a systematic review and meta-analysis of prospective studies. *Am Heart J.* 2013; 165(5):655–664.

Source of Support: None Declared
Conflict of Interest: None Declared