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A STUDY ON SERUM VITAMIN D LEVELS IN PATIENTS WITH DILATED CARDIOMYOPATHY

Cardiology

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ABSTRACT

INTRODUCTION: Vitamin D receptors are seen in vascular smooth muscle, endothelium, and cardiomyocytes. They are widely distributed in the cardiovascular system. Recent literatures have suggested a link between serum vitamin D status and heart failure and also an association between vitamin D level and left ventricular geometry.

AIM: Estimation of serum Vitamin D level in patients with dilated cardiomyopathy and to study relationship between serum Vitamin D concentration and the left ventricular dimensions and function in patients with dilated cardiomyopathy.

MATERIALS AND METHODS : Hundred consecutive patients with the diagnosis of the dilated cardiomyopathy were enrolled. Venous blood samples were collected in the morning after an overnight fast. The serum concentration of 25OHD3 was measured by radioimmunoassay and serum PTH concentration was assessed by immunoassay method. All patients underwent transthoracic Doppler echocardiographic examination. Standard apical four-chamber, parasternal short and long axis views of the LV were taken to determine echocardiographic parameters. 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 according to ASE guidelines 2015.

RESULTS: There were 38 females and 62 males, the mean age being 52±15.76. Among 38 females, 10 patients were diagnosed to be having peripartum cardiomyopathy. Of the 100 patients, 18 of them had type 2 diabetes mellitus and 28 patients had hypertension. The mean vitamin D level was 18.67±12.85 ng/ml (Range 3.70-73.66). Most of the patients had Vitamin D in the range of 10.01-20 ng/ml. Overall, 72 patients had severe LV dysfunction, 18 patients had moderate LV dysfunction and 10 patients had mild LV dysfunction. Mean Left ventricular end diastolic dimension (LVEDD) of the patients were 62.76±5.57 mm (Range 56-78 mm) and Left ventricular end systolic dimension was 53.12±5.84 mm (range 40-66 mm).

CONCLUSION: Patients with dilated Cardiomyopathy had their serum Vitamin D levels below normal levels. Patients with lower ejection fraction had lower levels of serum Vitamin D levels compared to patients with higher Ejection Fraction (EF).

KEYWORDS

Echocardiography, Ejection Fraction, LVEDD, 25(OH) vitamin D

INTRODUCTION:

Vitamin D, a steroid hormone, is 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. Vitamin D receptors have a wide distribution throughout the cardiovascular system including vascular smooth muscle, endothelium, and cardiomyocytes.

Recent studies reported that low vitamin D level is very common in the patients with heart failure and it is linked with poor prognosis.[1[[2] Additionally, studies suggest that there is a relationship between vitamin D and left ventricular geometry. Calcium has an essential role in myocardial contraction and hypocalcaemia that lead to congestive heart failure by reducing myocardial contractility. In the pediatric population it has been found that hypocalcaemia due to vitamin D deficiency is an occasional and reversible cause of the DCMP. Hypocalcaemic cardiomyopathy responds only to treatment with calcium and vitamin D.

There is consistent evidence that low serum 25OHD levels are associated with increased risk of cardiovascular diseases, including hypertension, coronary artery disease, heart failure, stroke, and type 2 diabetes. However, RCTs and Mendelian randomization studies so far have not succeeded in proving a benefit of vitamin D supplementation. Whether the deficiency of serum vitamin D level has a role in cardiovascular disease as a cause or etiology or just a marker of poor nutritional status in chronic disease is still unclear.[4] On this background, we undertook this study with an intention to investigate an association between vitamin D status and the dilated cardiomyopathy.

MATERIALS AND METHODS:

This hospital based observational study was carried out in Department of Cardiology of a tertiary healthcare centre and the duration of study was one year. All patients satisfying the inclusion and exclusion criteria and having given an informed consent to participate in the study were selected for the study. Ethical clearance was taken from Institutional Ethics committee.

Inclusion criteria were patients aged ≥ 18 years of age with an echocardiograph diagnosis of dilated cardiomyopathy.[5] Exclusion criteria were primary hyperparathyroidism, Chronic Kidney Disease, Chronic liver disease, Malignancy, Coronary artery disease, under hormone therapy, corticosteroid, and vitamin D supplementation, systemic inflammatory diseases. Since the study was defined by the duration of one year, sample size calculation was not required.

LABORATORY ANALYSIS:

Venous blood samples were collected in the morning after an overnight and the serum concentration of 25(OH)D3 was measured by radioimmunoassay. The serum PTH level was assessed by immunoassay method.

ECHOCARDIOGRAPHY:

All study population underwent transthoracic Doppler echocardiographic examination and were connected to an electrocardiogram monitor for recording their heart rate throughout the echocardiographic examination. Standard apical four-chamber, parasternal short and long axis views of the LV were taken to determine echocardiographic parameters. 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. 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

STATISTICAL ANALYSIS:

Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables and proportion (%) or frequency for categorical variables. The chi-squared test was used to analyze categorical data. Correlations between the variables were assessed by the Pearson coefficient analyses. A P value < 0.05 was considered as statistically significant. Statistical analysis was performed using the SPSS software package.

RESULTS

STUDY POPULATION:

Hundred consecutive patients with the diagnosis of DCMP according to the World Health Organization criteria were enrolled.

Table 1. Demographic And Clinical Characteristics Of The Patients

	MEAN	STANDARD DEVIATION (SD)	RANGE
AGE (in years)	53.3	±15.76	(21-90)
UREA (mg/dl)	40.86	±20.06	(15-150)
CREATININE	1.34	±0.87	(0.8-6.8)
Hb (gm/dl)	12.62	±2.07	(7.4-16)
Vitamin-D (ng/ml)	18.67	±12.85	(3.7-73.66)
PTH pg/ml	67.75	±33.30	(10-65)
LVEF (%)	31.30	±6.72	(25-50)
EDD (mm)	62.76	±5.57	(56-78)
ESD(mm)	53.12	±5.84	(40-66)
PASP (mm Hg)	45.88	± 15.94	(24-80)

**Hb-Hemoglobin in gm/dl, PTH- Parathormone, LVEF- Left Ventricular Ejection fraction, EDD-End diastolic diameter, ESD- End Systolic Diameter, PASP- Pulmonary artery systolic pressure.

Most of the patients were admitted in coronary care unit for evaluation and management. Out of the total 100 patients, 38 patients were female and 62 were males. The mean age of patients included in the patient were 52.38± 15.76 (Range 21-90 years). Among 38 females, 10 patients were diagnosed with peripartum cardiomyopathy. Out of 100 patients, 18 of them had type 2 diabetes mellitus and 28 patients had hypertension. Most of patients had some degree of mitral regurgitation (MR) at presentation. Out of the total 100 patients, 29 patients had severe MR, 30 patients had moderate MR, 38 patients had mild MR and remaining 3 had no MR. Seventy five patients were receiving diuretics in different forms; 15 patients were given diuretics after presentation. A statistically significant relationship was seen between left ventricular ejection fraction and serum vitamin D levels ($p<0.05$).

DISCUSSION:

The study found that most of the patients had Vitamin D in the range of 10.01-20 ng/ml. Vitamin D status of patients with DCMP was insufficient according to the current guidelines (the recommended threshold for sufficiency is ≥ 30 ng per milliliter). [6] Vitamin D exerts its effects in two ways, direct and indirect 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. Some earlier studies brought evidence forward that reduced serum calcitriol levels are the result of low circulating 25OHD levels.[7] It has recently been suggested that TNF-alpha may also suppress calcitriol synthesis. It has also been found that uptake of calcium into cultured cardiac muscle cells is increased by physiologic concentrations of 25OHD.[8] and intracellular accumulation of phosphate by muscle might be directly increased by 25OHD, an effect that may be blunted in the case of low circulating 25OHD level. 25(OH)D deficiency was an independent risk factor for hospitalization in patients with HF and the effect was found to be persisting in patients with frailty. [2]

Out of 100 patients, 18 had type 2 diabetes mellitus and 28 patients had hypertension. 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. The mean PTH level for the study group was 67.75±33.3 pg/ml (Range 11.7-157.1 pg/ml). 42 percent of the patients were having PTH level above the upper range or at a higher side of normal level. 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.[9][10][11] Furthermore, this deleterious impact of the PTH on the CV system still persists after the adjustment for 25OHD3, renal function and standard risk factors. [12] Therefore, another indirect preventive effect of vitamin D on myocardium is preclusion of excessive secretion of the PTH. Increased PTH level was independently associated with subclinical LV systolic dysfunction in patients with severe psoriasis.[13] Wannamethee SG et al. in their study reported that elevated PTH, but not $25OHD_3$ or other biomarkers of mineral metabolism, is associated with increased risk of incident heart failure.[14] PTH may contribute independently to myocardial dysfunction in patients with adults as has been reported in only a few cases to date. [15] 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. Lower serum calcium concentrations could be a reason for myocardial dysfunction in patients with DCMP. However, it was observed that significantly lower $25OHD_3$ concentrations accompanied by elevated PTH concentrations in the DCMP patients indicated that vitamin D deficiency underlies the hypocalcaemia. Thus, hypocalcaemia is

another indirect deleterious effect of vitamin D deficiency on cardiac function.

Ameri P et al reported that $25OHD_3$ was negatively correlated with LVESD and LV volume in patients with heart failure and also indicated that a significant nonlinear relation between $25OHD_3$ and LV concentric remodelling in community-dwelling subjects without heart disease. In this study a significant correlation was found between left ventricular diastolic end diastolic dimension and serum levels of vitamin D ($p<0.001$). Ameri P et al in their longitudinal study of aging showed higher circulating vitamin D concentrations were associated with favorable LV geometry and LV systolic function among older adults without cardiovascular disease. [16] Polat V et al in their study showed that vitamin D may play a key role in the LV remodeling and also found a positive association between $25OHD_3$ and LVEF, LV fractional shortening, stroke volume, cardiac output, and cardiac index in the DCMP patients. [17] The Thyroid function tests of most of patients were within normal limit. Some of the patients with dilated cardiomyopathy were also having associated pulmonary hypertension. Most of the patients received diuretics and also medicines for the primary cause. This also led to decrease in PASP. Diuretic therapy may have also contributed to the calcium ion levels. However, it is difficult to rule out that diuretic therapy of CHF patients has contributed to the low serum calcium levels. Spontaneous echo contrast is seen in echocardiography in conditions of stasis of blood inside cardiac chambers. Dilated cardiomyopathy (DCMP) is usually associated with decreased LVEF with resulting stasis of blood. In this study LV SEC was seen in 24 patients and a significant correlation was seen between the levels of serum vitamin D with left ventricular ejection fraction (LVEF). Patients with low serum vitamin D level were seen to have lower LVEF. Improving the level of serum vitamin D in these groups of patients may lead to improvement in EF. [18][19][20] Ten patients from the study were diagnosed to have peripartum cardiomyopathy (PPCMP) with low levels of vitamin D. Exact cause of PPCMP has not been established. However, nutritional deficiency is considered one of the causes. Zitterman A et al in their study found that a low vitamin D level was associated with activation of high TNF alpha system and also reported that patients with failing hearts had very low $1,25(OH)_2D$ and extremely high FGF-23 levels and treatment with calcitriol, has shown to regress cardiac hypertrophy. [21] Dalbeni A et al reported a substantial improvement in the ejection fraction after vitamin D supplementation for 6 months in elderly patients.[22] Gotsman I et al in their study shown 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.[23] 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.

STUDY LIMITATIONS:

DESIGN OF STUDY: This was an observational study wherein serum vitamin D level was assessed in patients of dilated cardiomyopathy single time. Longitudinal studies are needed to determine the temporal sequence of this association.

BIAS IN SELECTION:

The study being a hospital based study, there is always a chance of selection bias and subjects might not be the ideal representative of the population.

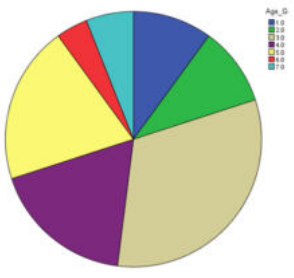

Figure 1: Diagram showing age distribution (groupwise). Blue segment (number 1) representing age group from 21-30 years of age, green (number 2) from 31-40 years of age, brown (number 3) from 41-50 years of age, purple (number 4) 51-60 years of age, yellow (number 5) 61-70 years of age, red (number 6) 71-80 years of age, light blue (number 7) 81-90 years of age

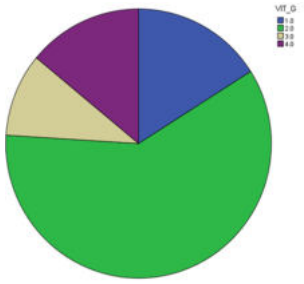

Figure 2: Diagram showing distribution of serum vitamin D levels in the study group. Blue (number 1) represents a serum vitamin D level of 0.01 to 10 ng/ml, green (number 2) represents a level of 10.01-20 ng/ml, brown (number 3) represents a serum vitamin D level of 20.01 to 30 ng/ml, purple (number 4) 30.01-40 ng/ml

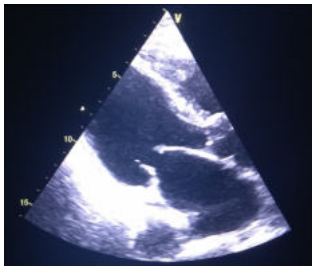

Figure 3: Parasternal Long Axis view showing dilated left ventricle in a patient of Dilated Cardiomyopathy (DCMP)

CONCLUSION

Patients with dilated cardiomyopathy had their serum Vitamin D levels below normal levels. Patients with lower ejection fraction (EF) had lower levels of serum Vitamin D levels compared to patients with higher Ejection Fraction (EF), and higher LVEDD is associated with lower vitamin D levels. Vitamin D supplementation can be considered in patients with dilated cardiomyopathy with reduced ejection fraction (EF) with proper follow up to assess the outcome.

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