Thesis

Vitamin D Deficiency and its Correlation with the Severity of Heart Disease in Dilated Cardiomyopathy Patients

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Abstract

Background: Cardiomyopathy is primarily a disorder of the cardiac muscle that causes myocardial dysfunction and is not the result of disease or dysfunction of other cardiac structures, systemic arterial hypertension and valvular stenosis or regurgitation.

Aim: The present study aimed to determine the prevalence of vitamin D deficiency and its correlation with the severity of heart disease in patients with dilated cardiomyopathy (DCMP).

Method: 70 ECHO-proven DCMP cases were enrolled from the medicine/cardiology department of LHMC & associated hospitals and ABVIMS & Dr. RML Hospital, New Delhi from November 2019 to October 2021. DCMP patients with ages more than 18 years who were willing to give consent and does not meet any of the exclusion criteria were enrolled in this study.

Results: Mean age of idiopathic DCMP patients was 48.3 ± 15.2. There were more males 48 (69%) than females 22 (31%). The mean ejection fraction was 26.6 ± 7.3, while the mean fractional shortening was 17.6 ± 3.1. Vitamin D deficiency was observed in 90% of patients, among which 68.5% were having moderate vitamin D deficiency and 10% were having severe vitamin D deficiency.

Conclusion: In our study, vitamin D levels were inversely correlated with the severity of heart disease in DCMP patients.

Introduction

DCMP is a progressive disease of the heart muscle i.e. a group of myocardial disorders characterized by dilatation of ventricles, contractile dysfunction of the left ventricle in the absence of chronic pressure and/or volume overload, and systolic dysfunction [1]. The 1980 WHO committee reserved the term cardiomyopathy for myocardial disease of unknown cause, but now there are multiple defined mechanisms e.g. ischemic, toxic, immunological, and metabolic, damaging the heart muscle leading to a common final outcome, represented as dilated cardiomyopathy. It occurs more commonly in males. It predominates in middle age and elderly age groups [2].

With the rapid advancement in molecular genetics and uncovering of underlying etiologies, DCMP is being recognized as a specific diagnosis and not one of exclusion. Due to increased awareness of this condition along with improvement in diagnostic techniques, it now accounts for the majority of all causes of heart failure. Depending on the diagnostic criteria...
used, the reported annual incidence varies between 5-8 cases per 1,00,000 population [3] and a prevalence of 1 case per 2700 (36 cases per 1,00,000) general population, accounting for 10,000 deaths and 46,000 hospitalizations in the United States annually [4].

Recently, the MOGE(S) classification system based on phenotype and genotype has been proposed which incorporates information on structural and functional abnormalities (M), organ involvement (O), genetics (G), etiology (E), and disease severity (S). However, it does not include certain cardiomyopathies as post-partum cardiomyopathy (PPCM) or risk of sudden death and is complex to use [5]. Idiopathic dilated cardiomyopathy (IDC) is essentially an exclusion diagnosis in patients with heart failure, who have met echo diagnostic criteria of DCMP without any obvious cause, as mentioned in the MOGE(S) classification. The clinical profile of DCMP at the time of presentation is highly variable, extending from no/minimal symptoms to progressive refractory heart failure.

Besides above mentioned aetiologies/mechanisms, the role of nutritional deficiencies is also documented. Hypocalcemic cardiomyopathy occurs possibly via a direct effect on cardiac myocyte contractility. It usually responds favorably to the restoration of normocalcemia but is refractory to the conventional management approach of heart failure [6]. Vitamin D also contributes to heart failure and cardiomyopathy by causing hypocalcemia [7]. In view of the high prevalence of vitamin D deficiency and chronic heart failure due to underlying DCMP with the lack of data on DCMP and possible prevention & treatment of these nutritional factors, this study is being done to determine the role of vitamin D deficiency in DCMP patients.

Materials and methodology

Our study was a hospital-based cross-sectional study conducted in Lady Hardinge Medical College & associated hospitals and ABVIMS & Dr. Ram Manohar Lohia Hospital, New Delhi. 70 ECHO-proven DCMP cases of age more than 18 years were taken from the medicine/cardiology ward/OPD of LHMC & associated hospitals and ABVIMS & Dr. RML Hospital, New Delhi from November 2019 to October 2021. Patients who had other serious co-morbid medical or surgical illnesses (sepsis, septic shock, Bariatric surgery, etc.), malabsorption syndrome, ulcerative colitis, and renal failure or who were already diagnosed with cancer or on cardiotoxic drugs such as doxorubicin, 5-FU, methotrexate, were excluded.

Each patient was then subjected to comprehensive clinical history taken by recall method along with the history of associated risk factors to rule out all possible etiologies to classify for idiopathic DCMP. The patients were then subjected to detail clinical examination followed by Chest X-Ray PA view, ECG, and Echo. Routine blood examinations including complete hemogram, liver function test, kidney function test, lipid profile, serum vitamin D, vitamin B12, calcium, and magnesium levels. Vitamin D detection was done with the chemilumiscence method on the Beckman Coulter DXI analyzer using commercial kits from Beckman Coulter.

ECHO

Transthoracic echocardiography (TTE) and Doppler studies were performed using machine Philips HD 11 XE. All standard (parasternal long axis and short axis, apical and subxiphoid) views were done. Also, doppler studies were performed and blood flow was recorded across all four valves. The following parameters were recorded: left ventricular dimension (LVEDD, LVESD), atrial dimension, left ventricular ejection fraction, left ventricular diastolic dysfunction (LVDD), and valvular regurgitation. LV systolic function was assessed by ejection fraction measured in M-mode at the mid-cavity level calculated by the software program built-in the echocardiography machine (normal range 50% - 70%).

Statistical analysis

The data was entered in Excel Spreadsheet and analysis was done using Stata (Texas, version 16.0). Continuous variables were represented as mean ± SD or median with IQR (Inter-quartile range). Categorical variables were represented as numbers and percentages (%).

The variables were tested for normality by the Kolmogorov-Smirnov normality test. All tests of significance were 2-tailed. The Chi2 test was used to check the association of categorical variables. Student t-test was used for checking the association between 2 continuous variables in a normal distribution. For non-parametric distribution, the wilcoxon rank sum test was used for testing this type of association. A sign rank test was used to check the association between 2 paired continuous variables. The strength of association was assessed using the Spearman correlation test. A p-value of < 0.05 was considered statistically significant.

Ethical statement

This study was approved by the institutional ethics committee, LHMC, New Delhi (No. 2019/39). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent was taken from all the patients.

Results

Among 70 DCMP patients, 48 (69%) were males and 22 (31%) were females. The mean age of DCMP patients was 48.3 ± 15.2 with 21 (30%) patients lie in the 41-50 years age group, followed by 17 (24.3%), 12 (17.1%), 9 (12.9%), and 11 (15.7%) in > 60, 51-60, 31-40 and < 30 year age group respectively. Mean BMI was 23.6 ± 2.57 kg/m², 40%, 34.3%, and 25.7% of DCMP patients were normal, overweight, and obese respectively.
All patients in this study were symptomatic i.e. having breathing difficulty (100%). Other symptoms in decreasing order of frequency were swelling of feet (85.7%), fatigue (50%), orthopnea (47.1%), paroxysmal nocturnal dyspnea (35.7%), palpitation (35.7%), chest pain (20%), and syncpe (5.7%). Maximum patients of both genders had NYHA class IV dyspnea at presentation followed by NYHA III with a \( p \)-value of 0.06 (Table 1). Mean respiratory rate, pulse rate, and systolic and diastolic blood pressure were 24.65 ± 5.01 /min., 111.85 ± 17 mm of Hg and 70.71 ± 12 mm of Hg respectively (Table 2). Hypertension was observed in 10%, diabetes in 14.3%, a history of alcohol (non-cirrhotic) in 10%, and a family history of DCMP in 2.9% of patients.

CP angle blunting was observed in 61 (87.1%) patients with a \( p \)-value of 0.52. There was evidence of cardiomegaly in 68 (97.1%) patients with a mean cardiothoracic ratio of 0.58 ± 0.02 with a \( p \)-value of 0.23. Sinus rhythm, normal axis, arrhythmia, bundle branch block, and ventricular hypertrophy were observed in 48 patients (68.6%), 41 patients (58.6%), 14 patients (20%), 18 patients (25.7%) and 11 patients (15.7%) respectively. All the patients included in this study were symptomatic i.e. having breathing difficulty (100%). The mean Hb was 11.6 ± 2.6 g/dl with anemia observed in 72.9% of patients. The mean TLP was 95780.0 ± 3995.1/mm³ and the mean platelet was 2.2 ± 0.9 lakhs/mm³. Mean bilirubin levels were 1.1 ± 0.8 mg/dl. Mean serum albumin was 3.5 ± 0.5 g/dl with hypoalbuminemia observed in 30% of patients with a \( p \)-value of 0.18. Leucocytosis, deranged LFT, and deranged KFT were observed in 25.7%, 20%, and 37.1% of DCMP patients respectively in our study. Median (IQR) serum AST and ALT values were 36 (27.3-53.8) IU/L and 37 (28-52) IU/L respectively. Median (IQR) serum urea and creatinine levels were 42 (36-55.25) mg/dl and 1 (0.8-1.27) mg/dl respectively. Mean TSH values were 4.5 ± 2.7 IU/ml with hypothyroidism observed in 5.7% of patients. Mean HDL levels were 36.2 ± 11.6 mg/dl, while mean LDL, TG, and cholesterol levels were 99.7 ± 49.7 mg/dl, 126.1 ± 71.8 mg/dl, and 158.1 ± 55 mg/dl respectively. Also, median (IQR) levels of HDL, LDL, T.G., and cholesterol were 37.5 (31-44.5), 91 (66-130.75), 110 (79-138.8), and 149.5 (120-199.75) respectively. There was evidence of dyslipidemia (22.9%) including hypertriglyceridemia (5.7%), low HDL (22.9%), high LDL (2.9%), hypercholesterolemia (7.1%) with a \( p \)-value of 0.53, 0.05, 0.07, 0.57, 0.57 respectively in our DCMP patients (Table 4).

Mean RBS was 147.4 ± 80.9 mg/dl and median (IQR) RBS was 120 (103-157) with evidence of hypoglycemia in 8.6% of patients with a \( p \)-value of 0.42. Mean serum sodium and potassium levels were 136.1 ± 6.6 mmol/l and 4.2 ± 0.6 mmol/l respectively with hypernatremia and hypokalemia observed in 11.4% and 10% respectively. It was seen that hyponatremia was significantly correlated with ejection fraction (Correlation coefficient = (-) 0.25). A negative coefficient implied that patients with hyponatremia were seen to have lower ejection fraction levels. The results were significant (\( p \) = 0.0368) (Table 4).

### Table 1: Clinical profile of DCMP patients (\( n = 70 \)).

<table>
<thead>
<tr>
<th>Breathlessness</th>
<th>Male (( n = 48 ))</th>
<th>Female (( n = 22 ))</th>
<th>Total (( n = 70 ))</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Yes</td>
<td>48 (69%)</td>
<td>22 (31%)</td>
<td>70 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: General examination parameters of DCMP patients (\( n = 70 \)).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Male (( n = 48 ))</th>
<th>Female (( n = 22 ))</th>
<th>Total (( n = 70 ))</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (mmHg)</td>
<td>25.64 ± 5.93</td>
<td>22.5 ± 8.28</td>
<td>24.65 ± 5.01</td>
<td>0.01</td>
</tr>
<tr>
<td>PR (mmHg)</td>
<td>103.04 ± 13.22</td>
<td>96.31 ± 16.77</td>
<td>100.92 ± 14.66</td>
<td>0.004</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>111.70 ± 15.7</td>
<td>112.18 ± 19.9</td>
<td>111.85 ± 17</td>
<td>0.000000</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70.79 ± 13.2</td>
<td>70.54 ± 9.1</td>
<td>70.71 ± 12</td>
<td>0.000000</td>
</tr>
</tbody>
</table>
Mean serum vitamin B12 levels were 373.13 ± 202.38 pg/ml with a p-value of 0.08 and median (IQR) of vitamin B12 levels of 311 (289-367) pg/ml with vitamin B12 deficiency was observed in 17.1% of patients. Mean serum calcium values were 8.84 ± 0.77 (male: 8.87 ± 0.84, female: 8.78 ± 0.60) with a p-value of 0.65 with median (IQR) serum calcium of 8.9 (8.5-9.37) with hypocalcemia in 40% patients. Mean serum magnesium levels were 1.78 ± 0.23 (male: 1.78 ± 0.25, female: 1.79 ± 0.18) with a p-value of 0.12 and median (IQR) vitamin D levels of 13.5 (11.42-17.37) pg/ml (Table 5).

Out of 70 dcmp cases, 90% had vitamin D def. with 78.5% patients had moderate-severe vitamin D deficiency (Figure 1). Vitamin D levels were correlated with ejection fraction and fractional shortening with a correlation coefficient of -0.102 and -0.105 respectively with a p-value of 0.40 and 0.38 respectively. A negative coefficient implied that patients with vitamin D def. were seen to have lower ejection fraction levels Table 6.

### Table 5: Lab. investigations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Male (n = 48)</th>
<th>Female (n = 22)</th>
<th>Total (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>17.0</td>
<td>8.25</td>
<td>16.84</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>344.6</td>
<td>148</td>
<td>282.17</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.87</td>
<td>0.84</td>
<td>8.78</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.78</td>
<td>0.25</td>
<td>1.79</td>
</tr>
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</table>

### Table 6: Correlation b/w ECHO parameters and vit. D deficiency.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Correlation Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>-0.102</td>
<td>0.402</td>
</tr>
<tr>
<td>Fractional shortening (FS%)</td>
<td>-0.105</td>
<td>0.385</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>-0.063</td>
<td>0.606</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>-0.101</td>
<td>0.404</td>
</tr>
</tbody>
</table>

### Discussion

A total of 70 patients who met the inclusion criteria were enrolled in the study. The data collected is non-parametric distributed.

### Age and gender

Kumar M, et al. [3], a study of a total of 60 subjects observed that 66.7% were males while 33.3% were females (M:F: 2:1) with a mean age of 48.3 ± 10.82 years. In a study by Kumar Divakar, et al. [8] of 30 DCMP patients, 56.6% were males and 43.25% were females with a mean age of 56.88 ± 15.99 years and 41.15 ± 20.19 years respectively. Boyilla Visalakshi, et al. [9], in a study of 60 DCMP cases observed that the majority of cases were above 60 years, comprised of 56.66% males & 43.33% females. Ushasree, et al. [10] in a study of 107 DCMP patients found that 71.96% of patients (adult) the ratio of adults male: female (M:F::2:1). Priya S, et al. [11] study of 116 subjects (56 DCMP patients vs. 60 controls), observed that mean age of DCMP patients was 48.6 ± 1.7 years. Polat Veil, et al. [12] study of 74 subjects (39 DCMP patients vs. 35 healthy subjects) observed 61.5% male and 38.5% female DCMP patients with a mean age of 50.4 ± 11.7 years.

Present study observations were consistent with the above-mentioned studies with peak incidence (30%) of DCMP patients seen in the age group 41-50 years age group with a mean age of 48.3 ± 15.2 years and 48 (69%) were males while 22 (31%) were females, out of 70 dcmp patients.

### Clinical features

Kumar Divakar, et al. [8] study included 30 DCMP patients, having dyspnea (exertional) present in all DCMP patients (100%). NYHA IV dyspnea predominates with 46.6% followed by NYHA III (33.3%), II (16.6%), and I (3.3%). Other symptoms were easy fatiguability (83.3%), pedal edema (70%), cough, palpitation, orthopnea, chest pain, abdominal pain, and syncope, present in DCMP patients. Kumar M, et al. [3] study of 30 DCMP studies demonstrated that there were 15 patients (50%) in NYHA class I, 14 patients in NYHA class II, and one patient in NYHA class III. Boyilla Visalakshi [9], et al. study of 60 DCMP patients observed that exertional dyspnea was present in all patients, followed by fatiguability (83.3%), pedal edema (70%), palpitation, orthopnea, chest pain, abdominal pain, and syncope, present in DCMP patients. Kumar M, et al. [13] study of 50 patients observed that dyspnea was seen in most of the patients (96%), followed by orthopnea (86%), edema (86%), fatigue (64%), chest pain (52%), palpitation (50%). Vanamali R.D, et al. [14] study of 37 DCMP patients observed that dyspnea (70%) was the predominant presenting complaint.

The current study findings were consistent with the above-mentioned studies as all patients were symptomatic i.e. having dyspnea (100%) with maximum patients having NYHA class IV (80%) followed by NYHA III (14.3%) class of dyspnea.
ECHO

Kumar Mukul, et al. [3] study of 30 DCMP studies demonstrated a mean LVEF of 30.47% having a significant difference from healthy controls of the same study. In a study, Kumar Divakar, et al. [8] of 30 DCMP patients reported mean LVEF as 30.87%. 40% of patients had EF of 20% - 29%, 36.6% had EF of 30% - 39%, 16.6% had EF of 40% - 45%, and 6.6% had EF of less than 20%. In a study of 60 DCMP cases by Boyilla Visalakshi, et al. [9] they demonstrated a mean LVEF of 30.87%. Sonowal N, et al. [14] in a study of 37 DCMP patients in N. East India observed a mean LVEF of 29.50% with a mean fractional shortening (FS) of 8.08% in their patients. The current study findings were also consistent with the above-mentioned studies with mean LVEF of 26.6 ± 7.3% and mean % FS of 17.6% ± 3.1% with more than half of patients having E.F. of < 30%, and % F.S. between 15% - 19.9%.

Vitamin D

Vitamin D regulates numerous processes involved in the pathogenesis of HF, such as cell proliferation and differentiation, apoptosis, oxidative stress, inflammation, endothelial function, vascular calcification, and activation of the renin-angiotensin system. Similarly, vitamin D plays a critical role in heart failure pathophysiology in dilated cardiomyopathy via the presence of vitamin D receptors and vitamin D-dependent calcium binding protein in cardiac muscle including endothelium, vascular and cardiac myocytes, thereby possessing an antihypertrophic effect on cardiomyocytes. Moreover, 1,25(OH)2 VitD3 also activates voltage-gated cardiac calcium channels, directly affecting cardiac contractile function or LV dimension, which can contribute to systolic dysfunction (i.e., reduced ejection fraction) in dilated cardiomyopathy [12]. Vitamin D is associated with functional status, illness severity, and prognosis in HF. This same study demonstrated a positive association between serum 25(OH) VitD3 levels (mean of 24.1 ± 10.4 ng/ml) and LV dimensions (i.e. mean LVEF of 27.6 ± 5.7%, mean fractional shortening of 13.1 ± 2.9) in DCMP patients. The current study is also consistent with the role of Vitamin D def. in dcmp as Vitamin D deficiency was observed in 90% of patients with a negative correlation coefficient b/w Vitamin D levels and EF levels.

Conclusion

Hypertension was observed in 10% diabetes in 14.3%, history of alcohol intake (noncirrhotic dose) in 4.3% and family history of dilated cardiomyopathy (DCMP) in 2.9% of patients as comorbidities. Vitamin D deficiency was observed in 90% of patients of which 78% had moderate to severe deficiency. Vitamin D could be the cause of DCMP which need to be corrected and follow-up of these cases should be done to assess the reversibility. Also in the current study, vitamin D levels were inversely correlated with the severity of heart disease in DCMP patients.

Limitations

No. of cases included in this study are less to have better statistical correlation and generalization of data i.e., needed more sample size. Follow-up of cases could not be done to assess the reversibility of etiologies of DCMP, as it was not part of this study.

References


