

Original Research Article

Study to determine serum vitamin D levels in patients with congestive heart failure

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Received: 19 September 2019

Revised: 28 September 2019

Accepted: 31 September 2019

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ABSTRACT

Background: It was to evaluate the association of serum levels of vitamin D in patients with congestive heart failure.

Methods: The present study was conducted in the department of Medicine at Chatrapati Shivaji Subharti Hospital among 100 patients, aged 18 years and above diagnosed as congestive heart failure on the basis of clinical and echocardiographic evidence. Clinical manifestations looked for CHF were: Dyspnea, orthopnea, acute pulmonary edema, cerebral symptoms, cheyne-stokes respiration, cyanosis, sinus tachycardia, raised jugular venous pressure, congestive hepatomegaly and pedal edema. In the present study deficiency/ insufficiency of vitamin D was considered when the presence of levels of 25-hydroxyvitamin D was <30 ng/ml. Laboratory tests performed to diagnose congestive heart failure and serum vitamin D levels were complete blood count, KFT (urea, serum creatinine), serum electrolytes, ECG, chest X ray and echocardiogram. Data were tabulated and examined using the statistical package for Social Sciences Version 22.0.

Results: When data was assessed for comparison in relation to NHYA grades and vitamin D levels, it was found to be statistically significant. The Mean±SD scores of serum urea (mg/dL) was found to be 44.7±56.4, 47.3±63.8 and 36.4±18.3 in whole study sample, vitamin D levels <30 and vitamin D levels >30 respectively with statistically significant difference. The Mean±SD scores of CPK MB (IU/L) was found to be 33.1±20.8 and 18.6±13.3 among the subjects having vitamin D levels <30 and vitamin D levels >30 respectively with statistically significant difference.

Conclusions: The results of the present study suggest that low levels of vitamin D may adversely affect the cardiovascular system.

Keywords: Echocardiogram, Heart failure, Hypovitaminosis, Vitamin D

INTRODUCTION

Congestive Heart Failure (HF) is a common cardiovascular condition with increasing incidence and prevalence.¹ Heart Failure (HF) is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or the ejection of blood.² Unlike western countries where heart failure is predominantly a disease of elderly, in

India it affects younger age group. The important risk factors for heart failure include coronary artery disease, hypertension, diabetes mellitus, cardiotoxic drugs, valvular heart disease and obesity.^{3,4} In India coronary artery disease, diabetes, hypertension, valvular heart diseases and primary muscle diseases are the leading causes for heart failure. Rheumatic heart disease is still a common cause of heart failure in Indians.⁵

Among the unfavorable epigenetic factors in relation to CVDs, vitamin D deficiency was found to be an important modifiable factor with the treatment where low levels of 25-hydroxyvitamin D were related to low birth weight, prematurity, increased perinatal mortality, and decreased glucose tolerance leading to unfavorable renal and cardiovascular outcomes in adulthood.⁶ Although the best-characterized sequelae of vitamin D deficiency involve the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system.⁷

The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population.⁸ Vitamin D receptors are present in vascular smooth muscle, endothelium, and cardiomyocytes and may have an impact on cardiovascular disease. Observational studies have shown a relationship between low vitamin D levels and blood pressure, coronary artery calcification, and existing cardiovascular disease.⁹

Cardiovascular effect of vitamin D can be grouped in to three: first vitamin D maintains balance between pro and anti-inflammatory cytokines.^{10,11} Secondly vitamin D decreases apoptosis and induce endothelial cell proliferation thirdly by association with Renin angiotensin aldosterone system.¹² Despite these clinical observations, prospective data are needed because vitamin D deficiency could be a consequence of cardiovascular disease rather than a cause. Hence, due to lack of data the present study was conducted to investigate the association of serum levels of Vitamin D in patients with congestive heart failure.

METHODS

The present study was conducted in the department of Medicine at Chatrapati Shivaji Subharti Hospital from April 2017 to December 2018. The study group was consisted of 100 patients, aged 18 years and above diagnosed as congestive heart failure on the basis of clinical and echocardiographic evidence. Patients were enrolled in the study after obtaining written informed consent and approval from Institutional Ethical Committee. The subjects were selected according to the following inclusion and exclusion criteria,

Inclusion criteria

- Clinical evidence of CHF (Raised JVP, pedal edema, congested hepatomegaly)
- Echocardiographic evidence of chamber dilatation with reduced/preserved ejection fraction with or without evidence of regional wall motion abnormality.
- All the patients with congestive heart failure with age >18 years.

Exclusion criteria

- Patients suffering from any other co-morbidity such as chronic kidney disease or chronic liver disease.
- Chronically malnourished patients/patients with known malignancies (paraneoplastic effect) or patients on chemotherapy.
- Patients receiving calcium/ vitamin D supplementation currently or in the recent past (6 months).
- CHF due to organic valvular heart disease.

The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, socioeconomic status, medical history and previous history of taking any medications and supplements.

Clinical assessment

Detailed clinical history including associated symptoms was noted. Detailed systemic examination of patients was done. Clinical manifestations looked for CHF were: Dyspnea, Orthopnea, Acute pulmonary edema, Cerebral symptoms like confusion, memory impairment, headache, insomnia and anxiety, Cheyne- stokes respiration- a type of periodic breathing with alternate periods of apnea and hyperventilation, Cyanosis, Sinus tachycardia, Raised Jugular venous pressure, Congestive hepatomegaly and Pedal edema.

Laboratory Investigation

Various laboratory tests were performed to diagnose congestive heart failure and serum vitamin D levels were assessed.

Complete blood count

A complete blood count was performed for all patients using a automated complete blood count analyzer and the following parameters were studied- haemoglobin, total WBC count, differential count, RBC count, MCV, MCH, MCHC, hematocrit and platelet count.

KFT

Urea - It is estimated using commercial test kit (Autozyme new blood urea, manufacturer Accurex Biomedical private limited, Thane, India, kit) Normal range vary from 2.5 to 7.1 mmol/L. High blood urea of greater than 10.0 mmol/L is termed Uremia which could be indicative of Congestive heart failure.

Serum creatinine - Measurement of Serum Creatinine was performed by Autozyme new serum creatinine, manufacturer Accurex Biomedical private limited, Thane, India, kit. A normal level of creatinine in the blood for

males and females is 0.6 to 1.2 mg/dl and 0.5 to 1.1 mg/dl respectively. High serum creatinine levels are indicative of congestive heart failure.

Serum electrolytes

Subjects with heart failure may show hyponatremia, magnesium, and potassium deficiencies; the latter two play a pivotal role in the development of cardiac arrhythmias.

ECG

Evaluate for arrhythmia as evidence of previous myocardial infarction. High precordial QRS voltage, poor precordial R wave progression and low limb lead voltage is said to have high specificity in diagnosis of Heart failure.

Chest X ray

Echocardiogram

Used to confirm diagnosis and to classify heart failure (heart failure with preserved ejection fraction [HFpEF], heart failure with reduced EF [HFrEF]).

Serum Vitamin D levels

To examine the association of Congestive heart failure and serum vitamin D levels. 25-hydroxyvitamin D lower than 30 ng/mL was considered as deficient according to Endocrine Society National Osteoporosis Foundation, International Osteoporosis Foundation, and American Geriatric Society. In the present study deficiency/insufficiency of vitamin D was considered when the presence of levels of 25-hydroxyvitamin D was <30 ng/ml.

Statistical analysis

Data were tabulated and examined using the Statistical Package for Social Sciences Version 22.0 (IBM SPSS Statistics for Mac, Armonk, NY: IBM Corp, USA). Descriptive statistical analysis had been carried out in the present study. Results on continuous measurements are presented as Mean±SD. Categorical data has been presented as frequency distribution. The statistical power calculation was based on the assumption that the data were normally distributed, p-value of <0.05 was considered as significant. Difference between two groups was determined using chi square test and student t- test for categorical data and continuous data respectively.

RESULTS

The mean±SD scores of age (years) were found to be 53.1±11.19, 51.5±10.7 and 58.3±11.30 years in whole study sample, vitamin D levels <30 and vitamin D levels >30 groups respectively. The present study revealed that

in relation to age, there was statistically significant difference found in comparison with vitamin D levels (p value <0.001) (Table 1).

Table 1: Age distribution among the study population.

Variables	Age (years)	
	Mean	SD
Whole study sample	53.1	11.19
Vitamin d <30	51.5	10.7
Vitamin d >30	58.3	11.30
Unpaired t test	21.93	
p value	0.001*	

p value<0.05 is considered as significant (#: Non-significant, *: Significant)

The present study comprised of 100 patients among them 51 males and 49 females were enrolled in complete study sample, 39 males and 37 females were found to have vitamin D levels <30. In addition, 12 males and 12 females were found to have vitamin D levels >30. When data was compared in relation to gender with Vitamin D levels, it was not found to be statistically significant (Table 2).

Table 2: Gender distribution of study population.

Variables	Sex			
	Male		Female	
	N	%	N	%
Whole study sample	51	51	49	49
Vitamin d <30	39	51.3	37	48.7
Vitamin d >30	12	50	12	50
Chi square test	0.012			
p value	0.993#			

p value<0.05 is considered as significant (#: Non-significant, *: Significant)

Table 3: Association of NYHA grades with vitamin D levels.

Variables	NYHA grades							
	1		2		3		4	
	N	%	N	%	N	%	N	%
Whole study sample	19	19	54	54	25	25	2	2
Vitamin D <30	8	10.6	41	53.9	25	32.8	2	2.7
Vitamin D >30	11	45.8	11	45.8	1	4	1	4
Chi square test	18.52							
p value	0.005*							

p value<0.05 is considered as significant (#: Non-significant, *: Significant)

The frequency distribution of NHYA grade 1 was found among 19, 8 and 11 patients in whole study sample,

vitamin D levels <30 and Vitamin D levels >30 respectively. Grade 4 was distributed as 2, 2 and 1 patients in whole study sample, vitamin D levels <30 and vitamin D levels >30 respectively. When data was assessed for comparison in relation to NHYA grades and vitamin D levels, it was found to be statistically significant (Table 3).

The Mean±SD scores of Serum Urea (mg/dL) was found to be 44.7±56.4, 47.3±63.8 and 36.4± 18.3 in whole study sample, vitamin D levels<30 and vitamin D levels >30 respectively with statistically significant difference. The present study revealed that in relation to Serum creatinine levels, there was statistically significant difference found in comparison with vitamin D levels (Table 4).

Table 4: Association of serum urea (mg/dL) and serum creatinine (mg/dL) with vitamin D levels.

Variables	Serum urea		Serum creatinine	
	Mean	SD	Mean	SD
Whole study sample	44.7	56.4	1.2	0.45
Vitamin D <30	47.3	63.8	1.1	0.49
Vitamin D >30	36.4	18.3	1.1	0.39
Unpaired t test	3.88		-25.75	
p value	0.001*		0.001*	

p value<0.05 is considered as significant (#: Non-significant, *: Significant)

The Mean±SD scores of CPK MB (IU/L) was found to be 29.9 ±19.9, 33.1±20.8 and 18.6±13.3 in whole study sample, vitamin D levels <30 and vitamin D levels >30 respectively with statistically significant difference found in comparison with vitamin D levels. When data was assessed for comparison in relation to Ejection fraction and vitamin D levels, it was found to be statistically significant (Table 5).

Table 5: Association of CPK MB (IU/L) and ejection fraction (%) with vitamin D levels.

Variables	CPK MB		Ejection fraction	
	Mean	SD	Mean	SD
Whole study sample	29.9	19.9	31	0.09
Vitamin D <30	33.1	20.8	27	0.07
Vitamin D >30	18.6	13.3	42.8	3.9
Unpaired t test	3.43		6.75	
p value	0.007*		<0.01*	

DISCUSSION

The implications of vitamin D deficiency extend far beyond the skeletal system of the human body. Vitamin D Receptors (VDRs) have been identified within the Cardiovascular (CV) system on Vascular Smooth Muscle Cells (VSMCs), renal juxtaglomerular cells, and cardiac myocytes.^{13,14} Vitamin D deficiency has been found to be

associated with increased incidence of Hypertension (HTN), Coronary Artery Disease (CAD), Myocardial Infarction (MI), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), and even Sudden Cardiac Death (SCD).¹⁵

Current understanding about vitamin D deficiency and HF is evolving. Epidemiologic studies show an 80% to 96% prevalence of vitamin D deficiency in HF, with increasing severity of HF associated with increasing severity of vitamin D deficiency. A pathophysiologic role has been suggested in rat models that associates hypertrophy and HTN with vitamin D deficiency. Prospective studies on vitamin D correction show positive results in rat models, but this finding has not been demonstrated in human trials. While this may be due to study design, it is also possible that vitamin D plays a major role in diastolic HF, plays a role in end-stage HF, or that vitamin D is merely a risk factor or predictor in HF. Most importantly, further studies need to be conducted before a final conclusion can be reached.¹⁶

In the present study, the patients with age >18 years were recruited which could eliminate the possible confounding factors due to ageing. The study suggested statistically significant association of ageing with vitamin D levels (p value=0.001). The results were found in accordance with the previous investigation stated by Melamed et al¹⁷ which depicted that the rate of all-cause mortality of 13,331 adults >19 years from the NHANES III Linked Mortality Files (1988-994) was independently higher by 26% for individuals with low vitamin D levels (25[OH]D < 17.8 ng/ml) compared to the highest quartile.

The present study stated no statistically significant association of gender with vitamin D levels. The present findings were found to be in contrast to the investigation conducted by Melamed et al, as they depicted the association between 25(OH)D levels and mortality was more pronounced amongst women.¹⁸

This study had revealed statistically significant relation of NYHA scores with vitamin D levels (p value=0.005). These results were found to be in accordance with the study conducted by Cubbon et al, in addition Serum Urea, Serum Creatinine and CPK MB were also found to have statistical significant correlation with vitamin D levels.¹⁹ Abnormalities of the vitamin D-parathyroid (PTH) axis have a direct effect upon a wide range of mammalian cells including cardiomyocytes. Through increased urinary excretion of calcium and magnesium, enhanced by loop diuretic use, elevated aldosterone levels drive PTH release.²⁰ This response is exacerbated in people with 25[OH]D deficiency. The consequences of 25[OH]D deficiency and elevated PTH levels are calcium loading, with cardiomyocyte and skeletal muscle contractile dysfunction, cellular hypertrophy, oxidative stress, immune activation, endothelial dysfunction (including enhanced endothelin-1 release).^{21,22} These influences are reflected clinically with an increased risk

of hospitalization and worsening renal function. This could be a possible reason for higher serum urea and creatinine in vitamin D deficiency in patients with CHF.

In the present study, Ejection fraction was found to have statistically significant association with vitamin D levels (p value <0.001). These results were found to be in contrast with the findings depicted by Cubbon et al, However, the results of the present study were in accordance with the findings of Witte et al, which represented a dose-response relationship between vitamin D levels and LVEF (R = 0.05; p = 0.023).^{19,23} They stated that the serum vitamin D levels increased significantly in patients receiving vitamin D supplementation.

The strength of the study includes exclusion of patients with co-morbidities such as Chronic Kidney Disease or Chronic Liver Disease, Chronically malnourished patients/ patients with known malignancies (paraneoplastic effect) or patients on chemotherapy, CHF due to organic valvular heart disease. In addition, patients with calcium/ vitamin D supplementation in past 6 weeks were also excluded. These exclusions had eliminated the possible confounders, but it remains possible that the results could have been affected by residual confounders.

The limitation of the present study could be that all confounding factors could not be accounted like social background and lifestyle that are difficult to measure. For example, the main source of vitamin D is not nutritional, rather the result of skin sunlight exposure. Hence, patients with chronic disease, immobility and the elderly (who require more sun exposure to make the same amount of vitamin D as younger individuals) are at higher risk of 25[OH]D deficiency since they spend less time outdoors.²⁴

CONCLUSION

Vitamin D is an important prohormone for optimal intestinal calcium absorption for mineralization of bone. Although the best-characterized sequelae of vitamin D deficiency involve the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system. Further observational studies are needed to confirm these findings and establish the mechanisms underlying these observations.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Wadhera N, Kalra G, Gupta A, Singhal S, Jha SK. Study to determine serum vitamin D levels in patients with congestive heart failure. *Int J Res Med Sci* 2019;7:4762-7.