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Relation between Serum Levels of Vitamin D and Echocardiographic Determinants of Systolic and Diastolic Functions in Patients with and without Cardiorenal Syndrome

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ABSTRACT

Background: vitamin D is a fat-soluble vitamin; it has skeletal and non-skeletal functions. The effect of Vitamin D on CV disease had several mechanisms including elevated PTH and Calcium-phosphate metabolism. It decreases the pro- remodeling of Angiotensin II on the cardiomyocytes.

The Objectives: to study relation between serum levels of vitamin D and echocardiographic determinants of systolic and diastolic functions in patients with and without cardio-renal syndrome.

Patients and Methods: prospective study was conducted on 90 patients of all age groups and both sexes, admitted to Ain-Shams University hospital. The study included 3 groups of patients: Group 1: systolic dysfunction and renal insufficiency (30 patients), Group 2: systolic dysfunction only (30 patients). Group 3: renal insufficiency only (30 patients), in addition 10 healthy controls were taken as controls. Patients were subjected to full comprehensive echocardiography and KFT with estimation of creatinine clearance, and Vitamin D level that was statistically studied against echocardiographic parameters of cardiac systolic and diastolic function. **Results:** our study found that, compared to patients with normal vitamin D level, patients with vitamin D deficiency (defined as having vitamin D level <20 ng/ml) had significantly higher ventricular thickness (IVS, PW and mean wall thickness) (P value < 0.001), and higher LV mass which seems to be linked eventually to worse outcomes with no significant impact on worsening Diastolic dysfunction. A ROC curve was done revealing a sensitivity of 80% for the mean wall thickness (≥ 10 mm) to identify patients with vitamin D deficiency.

Conclusion: Vitamin D deficiency was associated with ventricular hypertrophy with worsening outcomes with no impact on diastolic function.

Key words: Vitamin D deficiency, Systolic heart failure, Diastolic dysfunction.

INTRODUCTION

Vitamin D is a fat-soluble vitamin. The classic role of vitamin D for maintaining bone health was recently extended by reports linking vitamin D deficiency to various other diseases, including arterial hypertension and diabetes mellitus.[(1)] It also turned out that the myocardium is an important target tissue for vitamin D-mediated effects on a genomic and non-genomic level .[(2)] Recent scientific evidence showed that vitamin D has 3 major potential protective mechanisms; First, experimental studies indicated that 1,25 (OH) vitamin D could directly suppress renin gene expression. Second, the presence in the cardiac muscle cells of vitamin D receptors, a calcitriol-dependent Calcium binding protein and calcitriol-mediated rapid activation of voltage-dependent calcium channels. Third, vitamin D deficiency triggers secondary hyperparathyroidism, which then directly promotes cardiac hypertrophy. [(3)]

However, despite the suggested relation between vitamin D deficiency and cardiac function, the relation between vitamin D deficiency and the echocardiographic predictors of cardiac functions in patients with heart failure, to the best of our knowledge, has not been studied yet. Accordingly, we aim to study the relation between serum 25-hydroxy vitamin D levels and parameters of cardiac systolic and diastolic function in patients with LV systolic heart failure.

PATIENTS AND METHODS

Patients: The study included 90 patients of all age groups and both sexes, admitted to Ain-

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Shams University hospital. The patients were classified to 3 groups:

Group 1: LV Systolic dysfunction and renal insufficiency (30 patients)

Group 2: LV Systolic dysfunction only (30 patients)

Group 3: Renal insufficiency only (30 patients)

In addition 10 healthy subjects were included as control group (where they??).

Inclusion criteria for patient group:

- Systolic heart failure defined as having symptoms and signs typical of heart failure in addition to reduced LVEF (less than 40%).
- Renal impairment defined as having creatinine clearance less than 60 mL/min.

Exclusion criteria:

- Patients with previous vitamin D supplementation.
- Patients with conditions known to cause Vitamin D deficiency e.g., malignancies, chronic liver disease, bowel disease causing mal-absorption, patients with hemodialysis, etc.
- Patients with marked poor echogenicity.
- Patients on hemodialysis.

Methods: ***All patients were subjected to:***

1- ***Thorough history:*** Thorough history taking including, onset of symptoms, aetiologyof heart failure, NYHA class on presentation to the hospital, risk factors including age, gender, hypertension, DM, dyslipidemia, cigarette smoking, and current medications, symptoms suggestive of renal impairment (e.g. Loss of appetite, general ill feeding, fatigue, itching, nausea and weight loss).

2- ***Full clinical assessment:*** for height and weight to calculate body mass index, signs of heart failure (e.g. sinus tachycardia, elevated Jugular venous pressure, third heart sound, pulmonary venous congestion, and peripheral edema) and signs of renal impairment (e.g. itching marks, acidotic breathing, edema).

3- ***Pelviabdominal US:*** for grading of nephropathy

4- ***Venous blood sampling:*** Samples were sent for laboratory measurements of 25(OH) vitamin D, Calcium, and Phosphorus, Sodium, Potassium and serum creatinine. Estimated Glomerular filtration rate was calculated using the Cockcroft-Gault equation.

5- Full comprehensive Echocardiographic examination

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 2.5 multi-frequency phased array transducer (Vivid 5 or 7, GE-Vingmed, Horton, Norway). Digital routine gray scale2-dimensional apnea from tissue Doppler cine loops from 3 consecutive beats will be obtained at end expiratory apnea from standard apical views at depth of 12-20 cm. gains settings was adjusted for routine gray scale 2 D and tissue Doppler cine loops will be obtained, including mid-LV short axis views at the level of papillary muscle and standard apical views (4-chamber, 2-chamber, and long-axis) sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate.

LV end-diastolic volume (EDV), LV end-systolic volume (ESV) and ejection fraction (EF %), and left atrial volumes were obtained with the modified biplane Simpsons method from apical 2- and 4-chamberimages.

The pulsed wave Doppler-derived trans-mitral flow profile and digital color tissue Doppler-derived mitral annular velocities were obtained from the apical 4-chamber view. The ratio of mitral flow early diastolic wave (E) to late diastolic atrial contraction wave velocity (A), or E/A ratio; and the E wave deceleration time was measured. In addition, the ratio of early diastolic mitral flow velocity to TDI-derived early diastolic mitral annular velocity (E/e') ratio was calculated.

Assessment of LV function:

LV systolic function was assessed by EF%, ESV, and TDI derided peak systolic velocity(s').

LV diastolic function was assessed using E/A ratio, E-DcT, E/e', left atrial volume, and

pulmonary venous indices.

C- Statistical analysis:

Categorical data were expressed as number and percent and compared using chi-square (X^2) test (%). Continuous data were expressed as mean± SD and were compared using student t-test or ANOVA test. Correlations were checked for echocardiographic parameters against vitamin D level using Person correlation coefficient. With the exclusion of parameters that show co-linearity, multivariate regression analysis was done to check for the best independent predictor of vitamin D level. Level of significance was accepted at P value < 0.05. The ability of different echocardiographic parameters to detect vitamin D level <20 ng/ml was done using receiver operator characteristics curve (ROC-curve), by which the best cut off value for prediction that shows best sensitivity and specificity was checked.

RESULTS

Comparisons between patients' subgroups regarding demographic Data (Table 1)

There was no significant difference regarding age or presence of Hypertension , or smoking .But there was higher Diabetic patients in group 3 (17 patients) compared to group 1 (15 patients) or group 2 (only 3 patients), which reflects the effects of DM on worsening KFT among the study population.

Comparisons between patients' subgroups regarding laboratory results (Table 2, 3)

1- Compared to group 2 (HF only patients), group 1 (HF+RF patients) had a significant lower Vitamin D level ,lower Sodium and Calcium levels, higher Potassium and Phosphorus levels.

2- Compared to group 3 (RF only patients), group 1 (HF+RF patients) had a significantly lower Vitamin D level, lower Sodium and Calcium levels, and higher Phosphorus levels. Both groups had no significant differences regarding creatinine and Potassium levels **(Figure1).** A significant difference between Vitamin D deficiency was noticed being higher in group 1 (96.7%) than group 3 (76.7%) and lesser incidence of deficiency in group 2 (43.3%) **(Figure 2).**

Comparisons between echocardiographic determinants of systolic, diastolic function and LV wall thickness according to vitamin D levels: (Table 4, 5)

1- **Regarding LV wall thickness and LV mass:** It was found that, compared to patients with vitamin D ≥20 ng/ml, patients with vitamin D level <20 ng/ml had higher IVS thickness (p<0.001) higher PW thickness (p<0.001), higher mean LV wall thickness (p<0.001), and non-significant change in LV mass **(Figure 3).**

2- **Regarding systolic parameters:** It was found that, compared to patients with vitamin D ≥20 ng/ml, patients with vitamin D level <20 ng/ml had higher average s' (p=0.006) **(Figure 4)**. While no significant difference regarding average ESV, ESD, EDV, EDD, and EF were not different.

3- **Regarding Diastolic parameters:** Compared to patients with vitamin D ≥20 ng/ml, patients with vitamin D level <20 ng/ml had a lower E wave (p=0.033), a higher A wave, that was not statistically significant (p=0.55), Lower E/A ratio that was not statistically significant and a significant higher A' (P-value= 0.28). There was no significant difference between both groups regarding LAV which marker for long term Diastolic dysfunction. Also there was no significant difference between average IVRT, E-DcT, E', E/e' and e'/a'.

Correlations between echocardiographic determinants of systolic, diastolic function and LV mass versus vitamin D levels: (Table 6)

1- Regarding Diastolic function: It was found a positive correlation between vitamin D with IVRT in **all patients group** (r=0.308, p=<0.003) **(Figure 5)** and similarly in **group 1** (r=0.363, p<0.049) and **group 2** (r=0.670, p<0.001). Contradicting this finding means a

negative correlation between Vitamin D level and e' (r=-0.292, p<0.005) in **all patients** group and in **group 1** (r=-0.659, p<0.001) **(Figure 6)** and E/e. but owing to lack of significant correlations between vitamin D and other diastolic parameters as LAV, average a', E wave velocity, A wave velocity, E/A ratio, E-DcT and e'/a', it is suggested that there are no consistent correlation between vitamin D and diastolic dysfunction.

2- Regarding systolic function: Vitamin D level correlated negatively with average s' velocity (r= -0.285, p<0.007) **(Figure 7)**, this was confirmed in group 3 patients (r= - 0.667, p<0.001).

3- Regarding LV wall thickness: There was a significant negative correlation between vitamin D and all parameters of LV wall thickness. In all **patients' group** a Significant negative correlation was also noticed for IVS thickness (r= -0.567, p<0.001) **(figure 8),** PW thickness (r= -0.691, p<0.001) **(figure 9),** mean wall thickness (r= -0.654, p<0.001) **(figure 10),** and LV mass (r=-0.304, p=0.004) **(figure 11),** this was evidenced in **group 1** for IVS thickness (r=-0.514, p=0.004), PW thickness (r=-0.800, p<0.001), mean wall thickness (r=-0.714, p<0.001), and LV mass (r=-0.609, p<0.001). And similarly in **group 2** for PW thickness (r=-0.480, p=0.007), mean wall thickness (r= -0.385, p=0.03), with a non-significant trend toward lower IVS wall thickness and LV mass and for **group 3** for IVS thickness (r=-0.833, p<0.001), PW thickness (r=-0914, p<0.001, **table 7**), mean wall thickness (r=-0.898, p<0.001), and LV mass (r=-0.594, p<0.001).

Echocardiographic independent Predictors of vitamin D:

By applying a multivariate linear regression model for predictors of vitamin D level among patients, it was found that IVS, PW and mean LV wall thickness were independent predictors of vitamin D deficiency, (beta= 0.546, 0.622, 0.629, p=0.001, <0.001, <0.001, respectively). Next, ROC-curve was initiated to check the ability of these variables to detect vitamin D less than 20ng/ml and it was found that mean wall thickness could do so with the best area under the curve (AUC). (AUC: 0.826, cut-off values: ≥10 mm, sensitivity: 80%, specificity: 72.3% respectively) **(Table6) (Figure12).**

DISCUSSION

Our study demonstrated that the prevalence of vitamin D deficiency (defined as a 25-OHD level less than 20 ng/ml),[4] is increased among patients with heart failure than in general population and is much increased in patient with combined Heart and renal failure compared to either Heart failure or renal failure alone.

The increased prevalence of vitamin D deficiency in heart failure is multifactorial. Heart failure itself can induce vitamin D deficiency by several mechanisms. Shane ***et al***. [6] had demonstrated decreased cutaneous photo-conversion of vitamin D in patients with severe heart failure who have difficulty ambulating and obtaining adequate sunlight exposure**.** Right ventricular failure cause intestinal edema leading to decreased Vitamin D absorption together with passive liver congestion that impairs the synthesis of 25-OHD, making less substrate available for downstream activated vitamin D production in the kidney **.**[7]

Finally Renal Insufficiency, that is prevalent in patients with Heart failure, decreased the enzymatic conversion of 25-OHD to the active form 1, 25(OH) 2D **.**[8]

In our study vitamin D was associated with increased LV wall thickness and LV mass, with a little effect on cardiac systolic function (at least early in the diseases).

Several studies had shown that 25 (OH) D deficiencies is a frequent finding in Essential hypertension patients and is independently associated with Left ventricular hypertrophy. In a study by Fallo et al. [9] on 62 newly diagnosed hypertensive, compared with 24 healthy normotensive sex-, age-, BMI-matched controls found that hypertensive patients with 25(OH) D deficiency, had higher prevalence of LVH than their 25(OH) D-sufficient counterparts with no differences between the two groups in blood pressure levels as well as in other biochemical

and hormone parameters. There was an inverse correlation between LV mass index and 25(OH) D levels. [9]

The association of vitamin D deficiency with LVH had several possible mechanisms. Increased PTH levels are associated with insulin resistance, inflammation, vascular stiffness, myocardial hypertrophy and fibrosis. Moreover, through activation of the 1-25-OH vitamin D nuclear receptor, vitamin D has been shown to suppress myocardial hypertrophy and abrogate the hyper contractibility of the myocardium that is observed with diastolic HF, this effect is attenuated in Vitamin D deficient patients. [10]

Whereas the association between vitamin D and LVH was proven, our study found no consistent correlation between vitamin D and Diastolic function. The studies investigating the effects of vitamin D on LV diastolic functions are controversial and mostly are not suggestive of possible relation **Anil Pandit *et al***. [11] conducted the first, large cross-sectional study attempting to examine any relationship between baseline Vitamin D levels and comprehensive echocardiography to study LV diastolic function at Mayo Clinic. A retrospective analysis of 1011 patients from 2005 to 2010 who had an echocardiogram and a serum Vitamin D level performed 1 month later. Patients were divided according to Vitamin D deficient and vitamin D sufficient groups. With the exception of Diabetes, Patient demographics and conventional CVD risk factors of hypertension, smoking history and clinical coronary artery disease presence were comparable in both groups. The main finding of this study showed that Vitamin D has no significant correlation with diastolic function. Even in Diabetics who constitutes a higher proportion of patients with diabetics in the group of vitamin D deficiency, neither the Doppler diastolic parameters of LV diastolic dysfunction (which may subjects to acute hemodynamic changes) nor LAVI (a surrogate marker of long-term diastolic dysfunction) were different between the study groups. Of note, the same study showed that there was a significant relationship between Vitamin D level and IVS and LV mass index after adjusting for age, hypertension and Vitamin D therapy status suggesting the role of Vitamin D level on ventricular remodeling. [11]

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Tables and figures

Table (1): Comparing demographic data between patients' subgroups

		HF+RF		HF		RF		Chi-square test	
		No.	%	No.	%	No.	%	X^2	P-value
Sex	Female	5	16.70%	4	13.30%	14	46.70%	10.629	0.005
	Male	25	83.30%	26	86.70%	16	53.30%		
Age*	Mean± SD	60.37±6.41		55.63±9.31		55.67±9.74		2.997	0.055
	Range	48–70		34–72		38–72			
NYHA class	1	1	3.30%	0	0.00%	30	100.00%	97.165	<0.001
	2	16	53.30%	26	86.70%	0	0.00%		
	3	11	36.70%	4	13.30%	0	0.00%		
	4	2	6.70%	0	0.00%	0	0.00%		
DM		15	50.00%	3	10.00%	17	56.70%	16.08	<0.001
Hypertension		13	43.30%	13	43.30%	15	50.00%	0.35	0.83
Smoking		19	63.30%	20	66.70%	16	53.30%	1.21	0.54
Dyslipidemia		4	13.30%	0	0.00%	9	30.00%	10.96	0.004

***Age was compared using One Way ANOVA Annova test**

Table (2): Comparisons between patients' subgroups regarding laboratory results

		HF+RF	HF	RF	P1*	P2▪	P3#
		No.=30	No.=30	No.=30			
BNP	Mean±SD	21.43±9.41	21.73±7.56	7.87±4.80	0.892	<0.001	<0.001
Vitamin D	Mean±SD	14.38±4.06	22.60±8.13	16.80±3.93	<0.001	0.023	0.001
creatinine	Mean±SD	2.17±0.51	1.33±0.19	1.98±0.39	<0.001	0.109	<0.001
Crcl.	Mean±SD	41.25±11.26	68.62±13.36	47.15±11.36	<0.001	0.048	<0.001
Na+	Mean±SD	123.70±5.02	126.83±3.11	135.50±5.60	0.005	<0.001	<0.001
K+	Mean±SD	4.57±0.55	3.93±0.35	4.64±0.36	<0.001	0.562	<0.001
Ca	Mean±SD	8.01±0.33	8.42±0.32	8.26±0.20	<0.001	0.001	0.026
Phosphorus	Mean±SD	7.67±2.28	4.02±1.19	6.22±1.32	<0.001	0.004	<0.001

***P1: comparison between group 1 (HF+RF) and group 2 (HF), ▪P2: comparison between group 1 (HF+RF) and group 3 (RF), #P3: comparison between group 2 (HF) and group 3 (RF)**

Table (3): Comparisons between patients' subgroups regarding vitamin D deficiency

Vitamin D	HF+RF		HF		RF		Chi-square test	
	No.	%	No.	%	No.	%	X^2	P-value
Deficient	29	96.70%	13	43.30%	23	76.70%	21.711	<0.001
Normal level	1	3.30%	17	56.70%	7	23.30%		

Table (4): Comparisons between echocardiographic measurements according to vitamin D levels-

		Deficient	**Normal level**	
		No. = 65	**No. = 25**	**p-value**
E' mean	Mean±SD	6.81 ± 1.67	6.04 ± 2.58	0.099
A' mean	Mean±SD	8.48 ± 2.91	7.00 ± 2.59	0.028
S' mean	Mean±SD	6.27 ± 1.81	5.06 ± 1.89	0.006
E(cm/sec)	Mean±SD	78.30 ± 24.03	90.66 ± 23.59	0.031
A (cm/sec)	Mean±SD	73.23 ± 28.17	69.08 ± 32.21	0.550
E-DcT (msec)	Mean±SD	179.82 ± 77.47	158.36 ± 63.30	0.220
E/A ratio	Mean±SD	1.33 ± 0.90	1.63 ± 0.94	0.170
E/e'	Mean±SD	12.10 ± 4.44	17.39 ± 8.26	0.090
E'/a'	Mean±SD	0.90 ± 0.38	0.92 ± 0.30	0.782
IVRT(msec)	Mean±SD	105.17 ± 23.79	114.24 ± 20.87	0.098
LAV	Mean±SD	73.43 ± 24.52	72.78 ± 17.51	0.904
EDV	Mean±SD	152.94 ± 58.74	144.27 ± 26.16	0.480
ESV	Mean±SD	91.38 ± 56.78	83.86 ± 27.81	0.529
EF	Mean±SD	44.46 ± 16.24	42.06 ± 14.95	0.523
IVS	Mean±SD	11.62 ± 2.71	9.48 ± 1.69	<0.001
PW	Mean±SD	12.02 ± 2.68	9.48 ± 1.90	<0.001
Mean wall thickness	Mean±SD	11.82 ± 2.58	9.48 ± 1.74	<0.001
LV mass	Mean±SD	289.88 ± 164.10	245.80 ± 82.21	0.204
EDD	Mean±SD	54.17 ± 8.07	55.60 ± 5.23	0.414
ESD	Mean±SD	42.54 ± 11.15	42.68 ± 6.56	0.953

Table (5): Correlations between laboratory results and echocardiographic findings versus vitamin D levels:

	Vitamin D							
	All patients		HF+RF		HF		RF	
	r	p-value	r	p-value	r	p-value	r	p-value
BNP	0.077	0.471	0.181	0.339	-0.057	0.765	0.186	0.325
Cr cl.	0.668	0.000	.423	0.020	.535	0.002	.537	0.002
Na+	0.084	0.431	0.155	0.412	-0.073	0.701	0.101	0.596
K+	-0.535	0.000	-0.352	0.056	-.587	0.001	-0.312	0.094
Ca	0.809	0.000	.712	0.000	.629	0.000	.917	0.000
Phosphorus	-0.738	0.000	-.759	0.000	-.517	0.003	-.658	0.000
e' mean	-0.292	0.005	-0.308	0.098	-.659	0.000	-0.006	0.976
a' mean	-0.109	0.307	0.143	0.452	-.468	0.009	-0.148	0.436
s' mean	-0.285	0.007	-0.146	0.440	-.667	0.000	-0.164	0.386
E(cm/sec)	0.119	0.266	-.412	0.024	0.210	0.266	0.270	0.149
A(cm/sec)	-0.062	0.561	-0.023	0.906	-0.206	0.275	-0.023	0.903
E-DcT (msec)	-0.100	0.350	0.232	0.218	-0.301	0.106	-0.105	0.582
E/A ratio	0.157	0.139	-0.164	0.386	0.349	0.059	0.322	0.083
E/e'	0.292	0.005	-0.229	0.223	.670	0.000	0.231	0.218
e'/a'	-0.052	0.628	-0.341	0.065	0.079	0.679	0.205	0.276
IVRT (msec)	0.308	0.003	.363	0.049	.670	0.000	-0.140	0.461
LAV	-0.061	0.570	-.376	0.040	0.027	0.889	0.231	0.219
EDV	-0.101	0.342	-0.341	0.065	-0.126	0.507	0.335	0.071
ESV	-0.085	0.423	-0.348	0.059	-0.201	0.286	.375	0.041
EF	0.023	0.830	0.212	0.260	0.160	0.400	-0.186	0.325
IVS	-0.572	0.000	-.514	0.004	-0.266	0.156	- 833	<0.001
PW	-0.691	0.000	-.800	0.000	-.480	0.007	-.914	<0.001
Mean wall thickness	-0.654	0.000	-.714	0.000	-.385	0.036	-.898	<0.001
LV mass	-0.304	0.004	-.609	0.000	0.006	0.973	-.594	0.001
EDD	-0.025	0.812	-0.321	0.084	-0.017	0.930	0.270	0.150
ESD	-0.102	0.337	-.477	0.008	-0.230	0.222	.378	0.039

Table (6): Sensitivity and specificity of ROC to predict Vitamin D level <20 mcg/ml.

	Cutoff point	**AUC**	Sensitivity	Specificity	PPV	NPV
Mean wall thickness	≥10	0.826	80%	72.31%	60.9%	87%

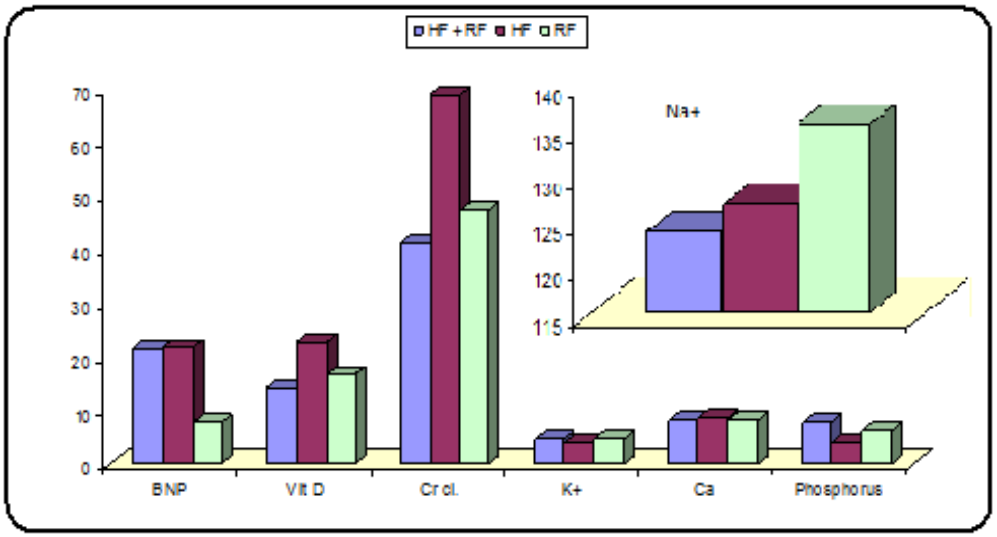

Figure (1): Comparisons between patients' subgroups regarding laboratory results

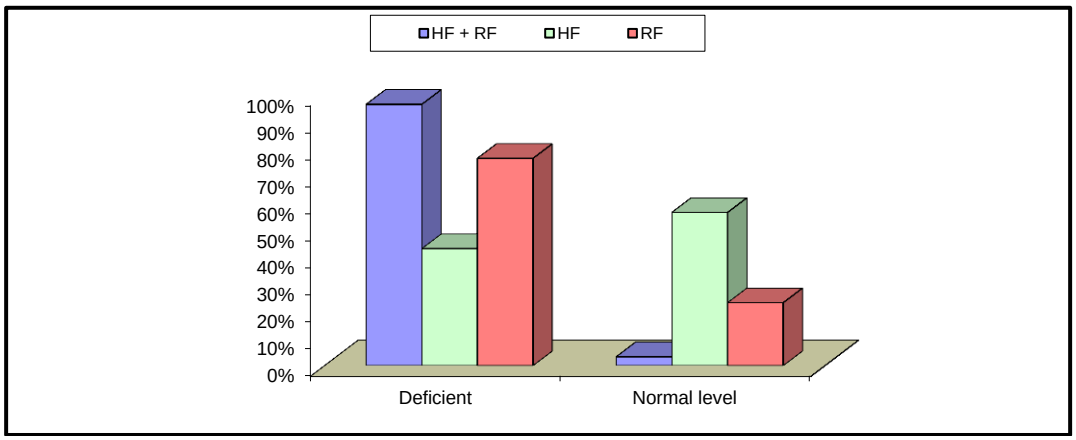

Figure (2): Comparisons between patients' subgroups regarding vitamin D deficiency

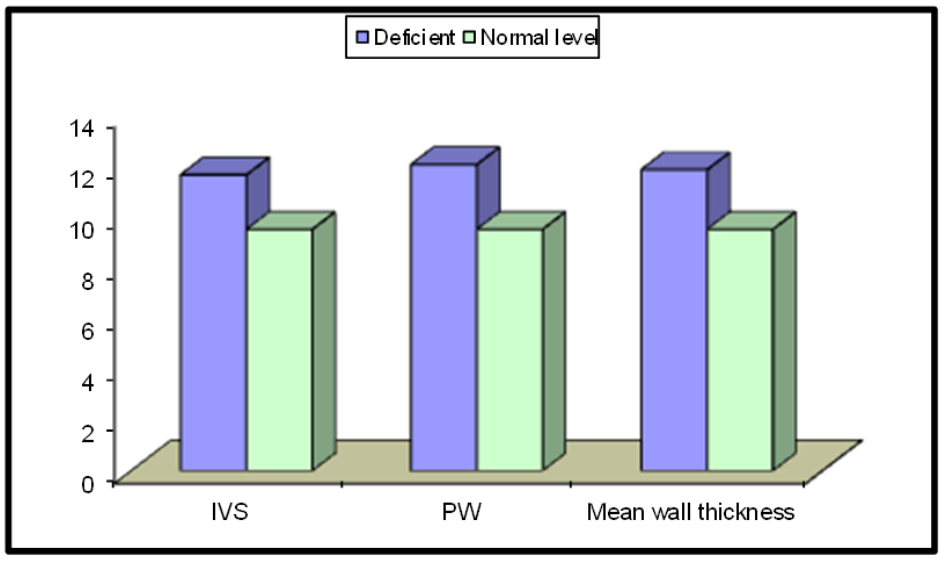

Figure (3): Comparisons between LV wall thickness according to vitamin D levels

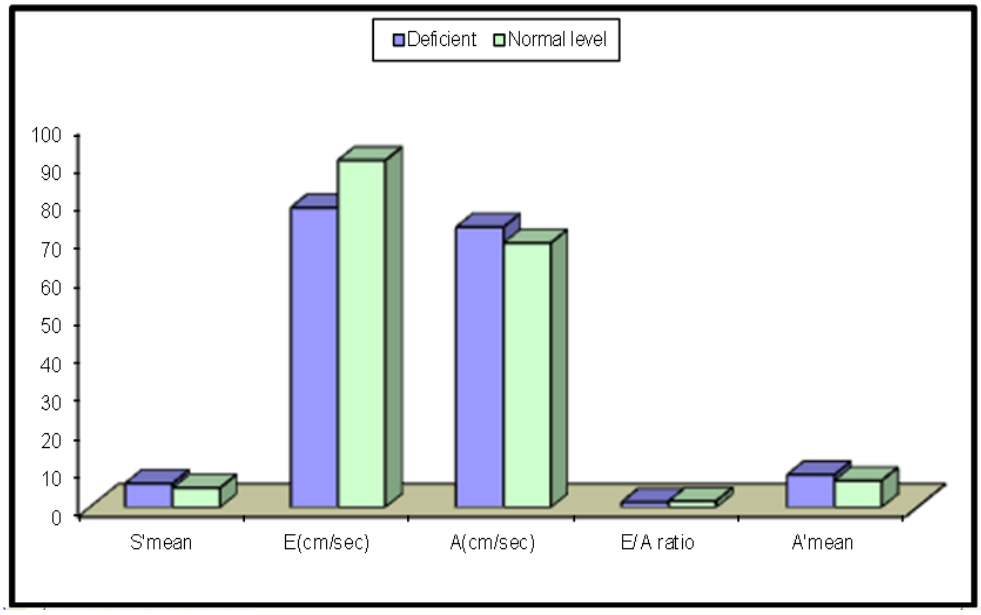

Figure (4): Comparisons between Doppler measurements according to vitamin D levels

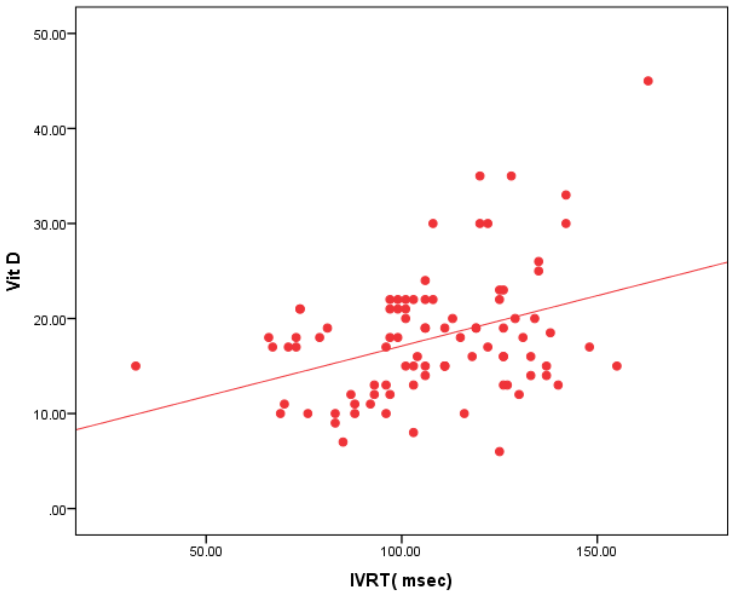

Figure (5): Correlations between vitamin D level and IVRT

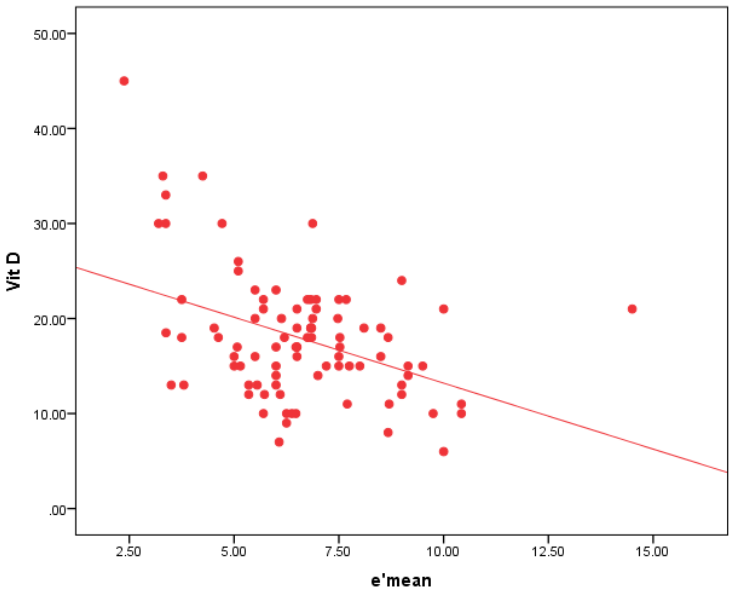

Figure (6): Correlations between vitamin D level and E'

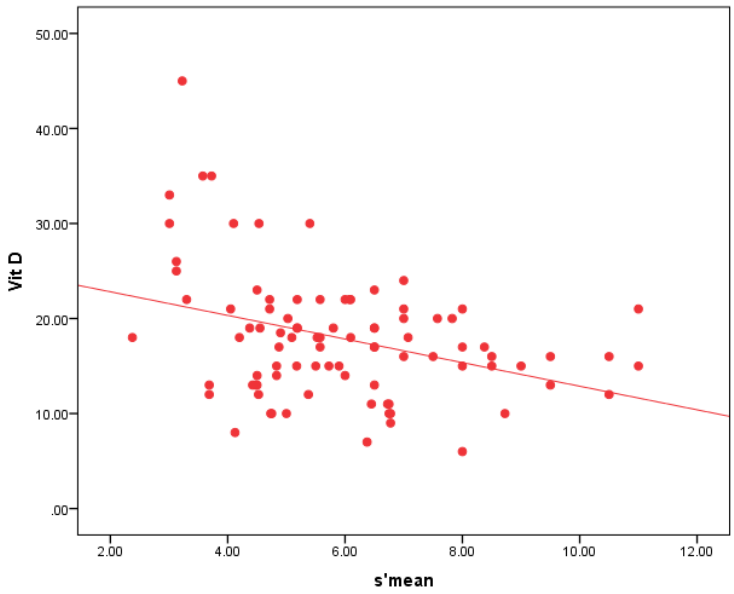

Figure (7): Correlations between vitamin D level and mean S´

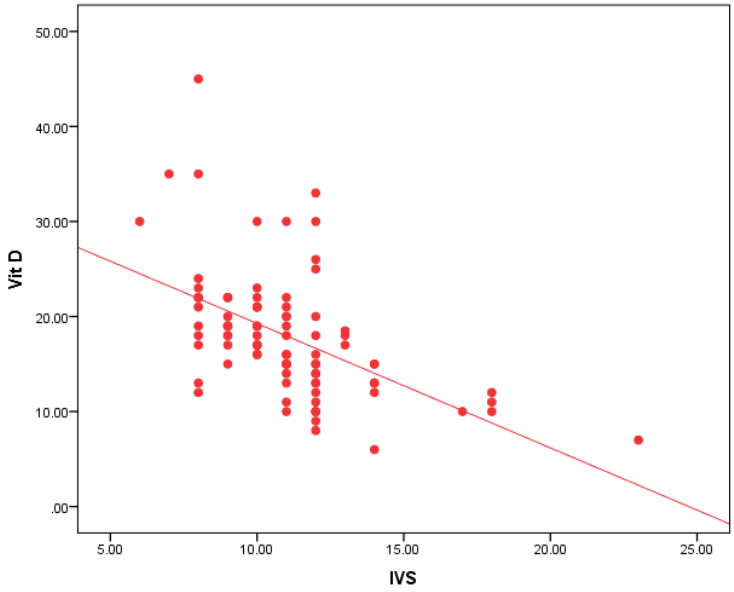

Figure (8): Correlations between vitamin D level and IVS thickness

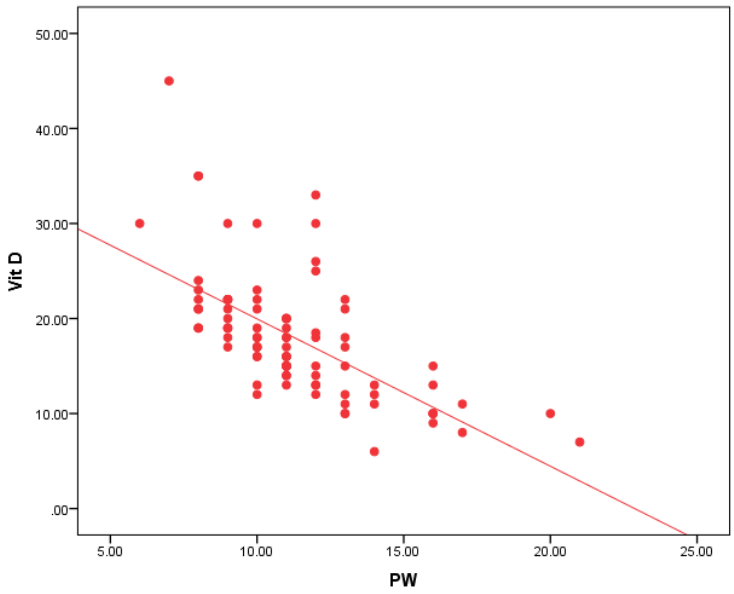

Figure (9): Correlations between vitamin D level and PW thickness

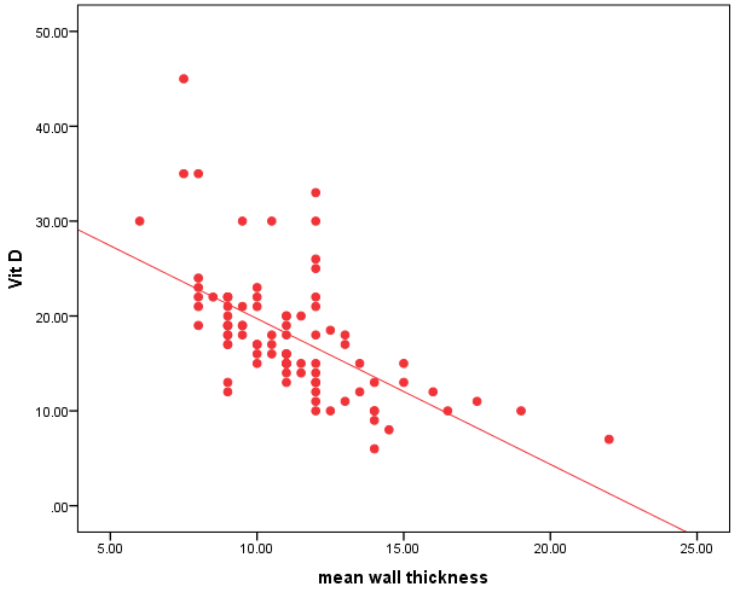

Figure (10): Correlations between vitamin D level and Mean wall thickness

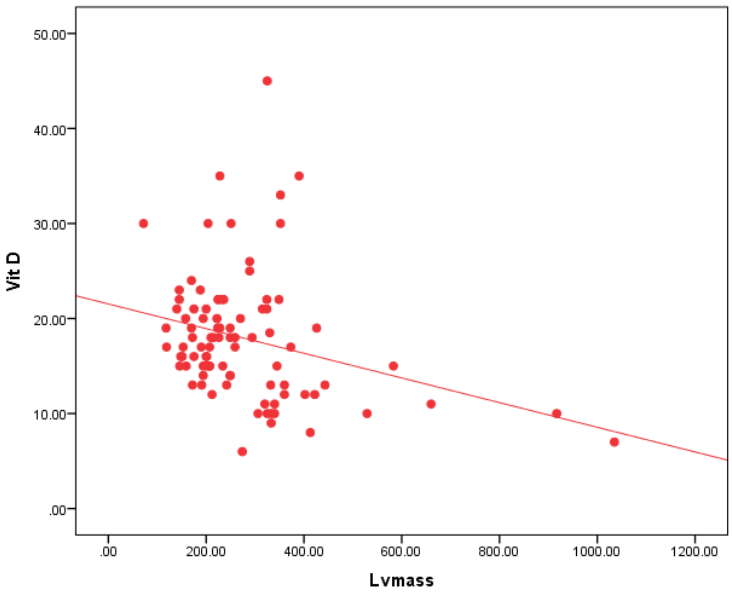

Figure (11): Correlations between vitamin D level and LV mass

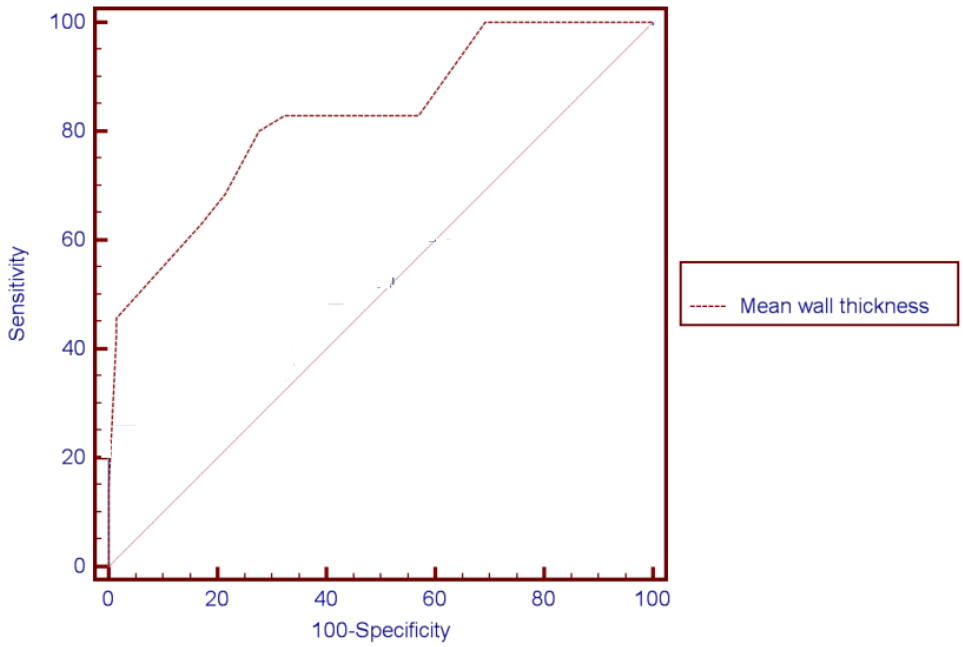

Figure (12): ROC curve for predictors of Vitamin D <20 mcg/ml.