Impaired Cardiac Functions and Aortic Elastic Properties in Patients with Severe Vitamin D Deficiency

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Abstract

Background: The study explored the effect of severe Vitamin D deficiency on cardiac functions and aortic elastic properties determined by echocardiography. Patients and Methods: It included 56 patients with Vitamin D deficiency (Group 1; 16 men, 40 women; mean age 43.1 ± 11.4 years) and 42 healthy individuals with normal Vitamin D levels (Group 2; 11 men, 31 women; mean age 40.0 ± 7.5 years). Calcium, parathormone, alkaline phosphatase, and Vitamin D levels were measured from blood samples, and all participants underwent echocardiographic examination. Results: Left ventricular diastolic functions were determined by both conventional and tissue Doppler methods and were found to be impaired in Group 1 compared to Group 2. Aortic distensibility was significantly reduced in Group 1 compared to Group 2, whereas aortic stiffness index was significantly increased. Left atrial active emptying volume and fraction (LAAEV and LAAEF) were significantly higher in Group 1 than in Group 2. There were significant negative correlations between Vitamin D level and LAAEV, LAAEF, and septal E/E’ ratio and significant positive correlations between Vitamin D level and septal, lateral, anterior, and right ventricular annular E’ velocities. Conclusion: In severe Vitamin D deficiency, echocardiographically assessed diastolic functions appeared particularly impaired, and ventricular and aortic elastic parameters were also adversely affected. In addition, LA mechanical functions were impaired, probably secondary to disturbed diastolic functions.

Keywords: Aortic elastic properties, diastolic dysfunction, echocardiography, Vitamin D

Introduction

Vitamin D deficiency occurs in 30%–50% of the adult population in developed countries. The deficiency is a known risk factor for various musculoskeletal system disorders, such as osteoporosis and osteomalacia, and its main causes are inadequate food and vitamin consumption, insufficient intestinal Vitamin D absorption, and reduced dermal Vitamin D synthesis. Animal studies have previously provided evidence that Vitamin D alters cardiac geometry and function. Vitamin D receptors have been identified in cardiac muscles, and animals that lack this receptor in their cardiomyocytes display cardiac cell hypertrophy. Experiments have shown an association between a low Vitamin D level and vascular dysfunction and activation of the renin–angiotensin system (RAS). The present study explored the association between Vitamin D deficiency and left ventricular (LV) diastolic function as well as aortic elastic properties and left atrial (LA) mechanical functions in individuals with normal systolic function.

Patients and Methods

Study population

This study included 56 patients with Vitamin D deficiency (Group 1; 16 men, 40 women; mean age 43.1 ± 11.4 years) and 42 healthy individuals with normal Vitamin D levels (Group 2; 11 men, 31 women; mean age 40.0 ± 7.5 years). Group 1 participants were selected from patients with any complaint who were admitted to the internal and family medicine polyclinics and had Vitamin D levels lower than 10 ng/mL. The study was conducted in winter, between October 2015 and March 2016. Participants with the following characteristics were excluded from the study: inadequate echocardiographic windows (to preclude the need for...
echocardiographic examination; LV dysfunction, structural heart disease (cardiomyopathy and valvular heart disease) evidenced by patient history, electrocardiography, exercise stress test, or echocardiography; current cardiac arrhythmia; or a history of atrial fibrillation, use of medications that affect cardiac conduction system, cerebrovascular disorder, secondary hypertension, or renal failure. Additional reasons for exclusions were the presence of thyroid function test abnormalities or a left bundle branch block shown by electrocardiogram. Individuals who were possibly using Vitamin D supplementation were also excluded, as were patients with lipid disorders because of the effect on aortic elastic properties. Smokers were instructed not to smoke on the testing day. Participants in Group 2 (control group) were selected from among healthy individuals who had no definitive diagnosis of any disorder and did not use any medication. All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki as revised in 2008. All participants gave informed written consent. The local ethics committee approved the study.

Biochemical analyses
A 10- to 15-ml fasting blood sample was taken through superficial veins of the forearm from each patient following an 8-h fasting period. Blood samples were centrifuged at 3000 rpm for 10 min to separate sera. Vitamin D levels (UniCel DxI 800, Beckman Coulter, Brea, CA, USA) and phosphorus, parathormone, calcium, and alkaline phosphatase levels were measured. In addition, fasting blood glucose, urea, creatinine, and lipid panel were also measured.

Echocardiography
Standard echocardiographic procedures were performed using a Philips EPIQ 7 device (Philips Healthcare, Andover, MA, USA). A 2.5-MHz probe was used for the Doppler measurements and a 2.5–3.5-MHz probe was used for tissue Doppler measurements. Measurements were made according to the American Society of Echocardiography guidelines, and average values were calculated from three cardiac cycles.[7] LV dimensions and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV end-diastolic diameter and end-systolic diameter and thicknesses of the interventricular septum and posterior wall of the left ventricle were measured. LV ejection fraction was estimated by Simpson’s rule. LA volume was calculated at end systole of the LV in the apical four-chamber view using the methods of disks (Simpson’s rule). Mitral inflow velocities were evaluated by pulsed wave Doppler with the sample volume placed at the tip of the mitral leaflets from the apical four-chamber view. Using the average of three beats, we measured diastolic peak early (E), peak late transmitral flow velocity (A), peak E-to-peak A velocities (E/A), and deceleration time of peak E velocity (EDT). Isovolumic contraction time, isovolumic relaxation time (IVRT), and ejection time were also measured.

LV-pulsed tissue Doppler imaging (TDI) was performed on the apical four-chamber view using a 5-mm pulsed Doppler sample volume with as little optimal gain as possible to obtain the best signal-to-noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. The sample volume was sequentially placed at the junction of the LV wall and the septal, lateral, anterior, and inferior mitral annulus and at the junction of the right ventricular (RV) wall and the tricuspid annulus for the four-chamber view. Myocardial peak systolic (S’) and peak early (E’) and late diastolic (A’) velocities of septum and lateral wall of the left ventricle and free wall of the right ventricle were measured. E/E’ ratios indicating diastolic function were separately calculated for lateral and septal annulus.

Left atrial mechanical function
LA volumes were measured by the disc method in the apical four-chamber view. LA volumes were measured as follows: just before mitral valve opening (maximal LA volume or \( V_{\text{max}} \)); at the onset of the P wave on electrocardiography (preatrial contraction volume or \( V_p \)); and at mitral valve closure (minimal LA volume or \( V_{\text{min}} \)).[7] All volumes were indexed according to body surface area (BSA) and expressed as milliliters per square meter. The stroke volume was calculated by subtracting the LV end-systolic volume (LVESV) from the LV end-diastolic volume (LVEDV). LVEDV and LVESV were calculated using the biplane method of discs in the apical four-chamber views at end diastole and end systole. The following LA emptying function parameters were also calculated: LA passive emptying volume = \( V_{\text{max}} - V_p \); LA passive emptying fraction = \( (V_{\text{max}} - V_p)/V_{\text{max}} \); LA active emptying volume (LAAEV) = \( V_{\text{max}} - V_{\text{min}} \); LA active emptying fraction (LAAEF) = \( (V_{\text{max}} - V_{\text{min}})/V_{\text{max}} \); conduit volume = \( (LVEDV - (V_{\text{max}} - V_{\text{min}})) \); and LA total emptying volume = \( V_{\text{max}} - V_{\text{min}} \).[9]

Aortic elastic properties
The ascending aorta was visualized by modifying the view in the parasternal long-axis window. M-mode echocardiographic recordings of the aorta were obtained from 3 cm above the aortic valve and used to measure aortic systolic and diastolic diameters (ASD and ADD). ASD was measured and recorded at the time point when the aortic valve widely opened at the end of systole and ADD at the time point corresponding to QRS peak. The mean values of at least three measurements were used for the comparisons and formulas in each participant. The markers of aortic elasticity, namely, aortic strain (AS), aortic distensibility (AD), and aortic stiffness index (ASI), were calculated using the following formulas and indexed by BSA.

\[
\text{AS} \% = 100 \times \frac{(\text{ASD} - \text{ADD})}{\text{ADD}}
\]

\[
\text{AD} \left( \text{cm}^2 \times \text{dy}^{-1} \times \text{atm}^{-1/2} \right) = \frac{(2 \times \text{AS})}{(\text{systolic blood pressure} - \text{diastolic blood pressure})}
\]

\[
\text{ASI} = \ln \left( \frac{\text{SBP}}{\text{DBP}} \right) / \text{AS}
\]

Statistical analysis
All statistical analyses were carried out using SPSS statistical software (version 18.0, SPSS, Chicago, IL, USA). Continuous variables are presented as mean ± standard
deviation. Categorical variables are presented as number and percentage. The Shapiro–Wilks test was used to evaluate the normal distribution of numerical variables. Independent samples t-test was used for the two-group comparison of the normally distributed variables, and the Mann–Whitney U-test for the two-group comparison of variables without normal distribution. A correlation analysis was performed for the relationship between continuous variables, and the analysis was interpreted using Spearman rank correlation coefficient. The confidence interval was set at 95%. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

Both groups were similar in terms of age, sex ratio, and body mass index [Table 1]. Although the mean SBP and DBP were higher in Group 1, the differences were not statistically significant [Table 1]. As expected, Vitamin D level was significantly lower in Group 1 compared to Group 2. LV diameters of both groups were similar. Interventricular septum and posterior wall thicknesses were significantly greater in Group 1 than in Group 2 although only the difference between interventricular septum thicknesses was significant [Table 1]. Among diastolic indices, mitral A wave and IVRT were significantly increased, whereas E/A ratio and IVRT were significantly lower in Group 1 than in Group 2 [Table 1]. E/E’ ratios measured from lateral and septal annulus were significantly greater in Group 1 than in Group 2 [Table 1]. E/E’ ratios measured from lateral and septal annulus were significantly greater in Group 1 than in Group 2 [Table 2]. There was a significant negative correlation between Vitamin D level and sepal E/E’ ratio \( (r = -0.32; P = 0.003) \).

The analysis of tissue Doppler parameters measured from five separate annuli revealed that E’ velocities measured from all annuli except for the lateral annulus were significantly lower in Group 1 compared to Group 2 [Table 2]. A’ velocities measured from all annuli were significantly greater in Group 1 than in Group 2 although the difference was statistically significant for the lateral and inferior annulus only [Table 2]. E’ velocities obtained from the septal, lateral, anterior, and RV annulus had a significant positive correlation with Vitamin D \( (r = 0.35; P = 0.001, r = 0.21; P = 0.048, r = 0.31; P = 0.005, r = 0.41; P < 0.001, \) respectively). None of the S’ values were significantly different between the two groups.

The analysis of aortic elastic properties showed that AD was significantly lower, whereas ASI was significantly greater in Group 1 than in Group 2. AS was lower in Group 1, with the difference having a trend for significance [Table 3]. A significant positive correlation existed between Vitamin D level and AD, and a significant negative correlation was found between Vitamin D and stiffness index \( (r = 0.28; P = 0.009, r = -0.29; P = 0.009, \) respectively). No significant correlation was found between Vitamin D level and AS.

The analysis of LA mechanical functions revealed that LAAEV and LAAEF were significantly greater in Group 1 than in Group 2. There were significant negative correlations between

**Table 1: Comparison of demographic features, laboratory parameters, left ventricular diameters, and conventional diastolic functions of the groups**

| Parameter                          | Group 1 \( (n=56) \) | Group 2 \( (n=42) \) | \( P \) |
|-----------------------------------|-----------------------|-----------------------|------|
| Age (years)                       | 43.1±11.4             | 40.0±7.5              | 0.12 |
| Gender (male)                     | 31                    | 31                    | 0.90 |
| BMI (kg/m²)                       | 28.6±5.85             | 27.1±2.7              | 0.12 |
| BSA (m²)                          | 1.79±0.19             | 1.84±0.17             | 0.14 |
| Systolic blood pressure (mmHg)    | 126.1±17.1            | 119.6±21.1            | 0.09 |
| Diastolic blood pressure (mmHg)   | 78.1±10.6             | 73.9±11.1             | 0.06 |
| Heart rate (beat/min)             | 75.1±7.4              | 72.5±6.9              | 0.11 |
| Vitamin D (ng/ml)                 | 7.32±1.72             | 44.6±15.20            | <0.001 |
| PTH (pg/ml)                       | 80.8±35.8             | 36.6±13.4             | <0.001 |
| Calcium (mg/dl)                   | 9.07±0.34             | 9.28±0.45             | 0.017 |
| Phosphorus (mg/dl)                | 3.20±0.42             | 3.1±1.2               | 0.47 |
| LVEDD (cm)                        | 4.49±0.40             | 4.62±0.29             | 0.089 |
| LVESD (cm)                        | 2.76±0.42             | 2.85±0.31             | 0.27 |
| IVS (cm)                          | 1.06±0.18             | 0.89±0.12             | <0.001 |
| PW (cm)                           | 0.96±0.16             | 0.91±0.11             | 0.08 |
| LA (cm)                           | 3.60±0.47             | 3.44±0.41             | 0.09 |
| EF (%)                            | 62.5±3.1              | 63.6±3.3              | 0.077 |
| Mitral E wave (m/s)               | 0.74±0.16             | 0.80±0.14             | 0.045 |
| Mitral A wave (m/s)               | 0.68±0.18             | 0.55±0.11             | <0.001 |
| Mitral EDT (ms)                   | 177.4±42.1            | 167.9±27.7            | 0.217 |
| E/A ratio                         | 1.17±0.40             | 1.52±0.44             | <0.001 |
| IVRT (ms)                         | 91.5±27.2             | 62.4±19.1             | <0.001 |

BMI=Body mass index, BSA=Body surface area, PTH=Parathormone, LVEDD=Left ventricular end-diastolic diameter, LVESD=Left ventricular end-systolic diameter, IVS=Interventricular septum thickness, LA=Left atrium, EF=Ejection fraction, PWT=Posterior wall thickness, EDT=E wave deceleration time, IVRT=Isovolumic relaxation time

**Table 2: Comparison of systolic and diastolic velocities of the groups**

| Parameter         | Group 1 \( (n=56) \) | Group 2 \( (n=42) \) | \( P \) |
|-------------------|-----------------------|-----------------------|------|
| Septal S’ (cm/s)  | 8.05±1.5              | 8.19±1.13             | 0.59 |
| Septal E’ (cm/s)  | 7.72±2.36             | 10.32±2.55            | <0.001 |
| Septal A’ (cm/s)  | 8.99±2.24             | 8.68±2.00             | 0.48 |
| Lateral S’ (cm/s) | 9.81±3.60             | 9.46±1.92             | 0.53 |
| Lateral E’ (cm/s) | 11.00±3.74            | 13.16±3.63            | 0.06 |
| Lateral A’ (cm/s) | 8.83±2.78             | 8.79±2.33             | 0.05 |
| Tricuspid S’ (cm/s) | 12.23±2.60         | 12.71±2.14            | 0.32 |
| Tricuspid E’ (cm/s) | 9.74±3.18            | 12.42±2.15            | <0.001 |
| Tricuspid A’ (cm/s) | 11.84±3.71         | 10.69±3.04            | 0.10 |
| Anterior S’ (cm/s) | 8.61±2.07            | 8.44±1.92             | 0.67 |
| Anterior E’ (cm/s) | 9.68±3.37            | 12.60±2.66            | 0.001 |
| Anterior A’ (cm/s) | 9.04±2.70            | 8.56±2.19             | 0.35 |
| Inferior S’ (cm/s) | 8.54±1.54            | 8.59±1.29             | 0.87 |
| Inferior E’ (cm/s) | 8.65±2.98            | 11.39±2.60            | 0.001 |
| Inferior A’ (cm/s) | 9.96±2.32            | 8.88±2.01             | 0.02 |
| E/E’ lateral      | 7.33±2.57             | 6.45±1.47             | 0.039 |
| E/E’ septal       | 10.15±2.70            | 8.31±2.14             | 0.001 |

S=Systolic myocardial velocity, E=Early diastolic velocity, A=Late diastolic velocity
Vitamin D level and both LAAEV and LAAEF ($r = -0.37$; $P = 0.001$, $r = -0.28$; $P = 0.12$, respectively).

**DISCUSSION**

The main finding of our study is that Vitamin D deficiency may affect various cardiac functions. In particular, diastolic function and aortic elastic properties are adversely affected by Vitamin D deficiency, which also affects some other echocardiographically detectable cardiac functions. Our findings may indicate subclinical cardiac involvement in Vitamin D deficiency.

Molecular animal and human studies have indicated that calcium and Vitamin D are closely associated with cardiovascular functions. Vitamin D deficiency is primarily caused by insufficient sunlight exposure, followed by inadequate dietary intake.

Although the exact relationship of Vitamin D with cardiovascular hemodynamics and its definitive role in the genesis of cardiovascular disorders are unknown, various mechanisms have been hypothesized. Some studies have indicated that Vitamin D has several affect to volume and blood pressure hemostasis by helping to reduce LV hypertrophy and regulating its functions through modulation of the RAS.

Vitamin D appears to play a role as an endocrine suppressor of renin biosynthesis. Specifically, in the context of Vitamin D deficiency, transcription of the Vitamin D receptor does not occur, and the lack of receptor, in turn, causes RAS overstimulation, which results in an increase of blood pressure and the development of cardiac hypertrophy.

shown that a high Vitamin D level was associated with better systolic functions and lower LV systolic diameter. Patange et al., in a study on children with chronic renal failure, found that Vitamin D deficiency was associated with increased LV mass and diastolic dysfunction. In another study, rats deprived of Vitamin D receptors exhibited cardiac hypertrophy, cardiac fibrosis, and increased muscle mass. Meems et al. demonstrated that Vitamin D receptor agonists influenced cardiac hypertrophy and fibrosis and exerted a protective effect related to reduced cardiac oxidative stress. We found impaired diastolic functions assessed by both conventional methods (E/A ratio, IVRT) and the tissue Doppler (E′/E″ ratio) method in the Vitamin D-deficient group. Although we did not investigate renin levels in our study, one of the causes of diastolic dysfunction could be an increase in renin levels in the Vitamin D-deficient group. Pandit et al. conducted a study of 1011 patients and found adverse findings. They divided the patients into two groups (Group 1 with serum Vitamin D level ≤20 ng/mL and Group 2 with serum Vitamin D level >20 ng/mL) and found no significant association of Vitamin D levels and LV diastolic performance, including LA volume index. The difference between these results and those of the current study may be explained by the Vitamin D levels included in our study being much lower.

Vitamin D deficiency is thought to increase the levels of some pro-inflammatory cytokines and reduce the levels of some anti-inflammatory cytokines, thereby adversely affecting cardiac functions and precipitating heart failure. In Vitamin D deficiency, pro-inflammatory cytokines such as interleukin (IL)-8 and tumor necrosis factor-α (TNF-α) are activated. In addition, Vitamin D appears to suppress a pro-inflammatory milieu by downregulating nuclear factor-xB and reducing the production of IL-6, IL-12, interferon-C, and TNF-α. Furthermore, reduced Vitamin D levels have also been shown to be correlated with the levels of N-terminal pro-b-type and N-terminal pro-atrial natriuretic peptides, which are thought to lead to heart failure. Similarly, an inflammatory environment resulting from an impaired adaptive immune response due to severe Vitamin D deficiency leads to vascular dysfunction and insulin resistance. Since this possibility fell outside the aim of our paper, we did not evaluate inflammatory markers in our patients.

The studies exploring the association between hypertension and Vitamin D have yielded conflicting results. Large-scale cross-sectional studies have shown a negative correlation between Vitamin D and blood pressure. In the National Health and Nutrition Examination Survey study of 12,644 individuals, SBP was lowest in individuals with the highest Vitamin D levels and vice versa. Similarly, in a large-scale study, Hintzpeter et al. showed that Vitamin D levels were lower in women with hypertension and cardiovascular disorders. In contrast to these findings, however, some authors have not found any association between hypertension and Vitamin D. In a recent study by Di Nora et al. showed similar contrast findings. Although they did not investigated Vitamin D levels,
their study revealed that higher SBP (>120 mmHg) may be associated with a better cardiovascular outcome compared to lower SBP (<120 mmHg). Our study population consisted of participants without a history of hypertension or the use of any medications for its treatment. However, participants in Group 1 who had Vitamin D deficiency had higher blood pressure than controls. Given that our participants had no overt hypertension, a possible hypothesis is that high blood pressure readings were correlated to Vitamin D level through the previously mentioned mechanisms. Previous clinical trials have yielded conflicting results regarding the relationship between Vitamin D and aortic elastic properties. Some authors have reported that Vitamin D exerts adverse effects by increasing arterial calcification, whereas other others have argued that it may exert some beneficial role. Wong et al. investigated the effect of Vitamin D on aortic functions and concluded that Vitamin D effectively preserves the structure of elastic fibers and the ratio of elastic fibers to collagen fibers in the artery media. This issue may be one of the factors underlying the impairment of aortic elastic properties. We found impaired aortic elastic properties in individuals with Vitamin D deficiency compared to those without the deficiency. The significant correlations between Vitamin D and AD and stiffness index suggest that low Vitamin D levels are associated with impaired aortic elastic properties. Although the blood pressure measurements are not statistically significant between the groups, high DBP may also contribute to impaired aortic elastic properties.

LV diastolic dysfunction is traditionally evaluated by Doppler patterns obtained from mitral inflow. Depending heavily on preload reduces the reliability of these parameters in various scenarios. Evaluation of diastolic functions by tissue Doppler is less preload dependent and thus more reliable. In our study, the early diastolic velocities obtained from all annuli except for the inferior annulus were significantly lower in Group 1 compared to the control group. Diastolic functions assessed by both conventional methods (E/A ratio, IVRT) and tissue Doppler (E’ velocity and E/E’ ratio) were significantly impaired in the Vitamin D-deficient group compared to the controls. These findings suggest that normal ejection fraction with low Vitamin D levels is correlated to impaired diastolic functions.

The left atrium functions as a reservoir during systole, a conduit during early diastole, and an active contractile chamber in late diastole. LA function mechanically facilitates the transition between flow through the pulmonary venous circulation and the intermittent filling of the left ventricle. During diastole, the left atrium is directly exposed to LV pressure, which increases when LV diastolic function is impaired. In our study, LAAEV and LAAEF were significantly increased in patients with Vitamin D deficiency compared to those without. In addition, there was a negative correlation with Vitamin D levels. Increased LA active contraction volumes may be due to limited LV filling. We suggest that the hearts of participants with Vitamin D deficiency may be attempting to compensate for impaired LV filling through a more vigorous atrial contraction.

The major limitation of our study is that we obtained instantaneous blood pressure readings before the echocardiographic examinations. Ambulatory blood pressure measurement may have yielded more accurate blood pressure readings. In our study, none of the participants have been diagnosed hypertension. Even if the blood pressure measurements are not statistically significant between the groups, high DBP may also contribute to echocardiographic findings. Further, assessing whether cardiac and vascular pathologies detected by echocardiography would recover after Vitamin D replacement may have increased the accuracy of our results. LA mechanical function was assessed using the disc method. LA volumes could have been confirmed by the elliptical method. However, the elliptical method also requires M-mode measurements and has several disadvantages associated with M-mode border detection. Small sample size may be another limitation of our study.

**Conclusion**

Echocardiographically assessed diastolic functions may be particularly impaired in Vitamin D deficiency, which may also affect ventricular myocardial velocities and aortic elastic properties. In addition, LA mechanical functions are also impaired, probably due to disturbed diastolic functions, and blood pressure increase may augment these perturbations. Such echocardiographically detected pathologies may be signs of subclinical cardiac involvement in Vitamin D deficiency. Large-scale studies investigating the impact of Vitamin D replacement on these parameters are needed to verify our results.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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