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Evaluation of the Relationship Between Vitamin D Deficiency and Subclinical Cardiac Dysfunction Using 2D/3D Strain Echocardiography in Healthy People

Aim	Vitamin D deficiency has a high prevalence in the population and is highly associated with cardiovascular diseases. The aim of this study was to evaluate subclinical left ventricular (LV) function using strain analysis in healthy individuals with vitamin D deficiency.
Material and methods	113 healthy volunteers were enrolled in the study (age, 44.1±7 yrs, 34 male). All volunteers underwent two-dimensional (2D) and three-dimensional (3D) speckle tracking echocardiography after conventional echocardiographic evaluation. The subjects were divided into two groups according to their vitamin D concentrations. 61 subjects with vitamin D less than 20 ng/ml were included in the vitamin D deficiency group. The baseline clinical characteristics, laboratory measurements, echocardiographic data, including 2D and 3D global longitudinal strain (GLS) values, were compared between the groups.
Results	The 2D GLS values of the subjects with vitamin D deficiency were lower (mathematically less negative) than subjects with normal vitamin D (–16.1±3.4 vs –19.3±4.2, p<0.001). Similarly, the 3D GLS results were lower in subjects with vitamin D deficiency (–18.3±5.2 vs –24.1±6.9, p<0.001). A significant correlation was detected between the vitamin D concentrations and the 2D and 3D GLS measurements. (r=0.765 and r=0.628, respectively, p<0.001). Vitamin D was found to be an independent predictor of impaired 2D and 3D LV GLS (p=0.031, p=0.023, respectively).
Conclusion	Subclinical LV dysfunction in healthy individuals with vitamin D deficiency was demonstrated by 3D and 2D strain analysis. Due to potential negative effects of vitamin D deficiency on cardiac function, more attention should be paid to healthy individuals with vitamin D deficiency.

Keywords	Vitamin D; heart failure; global longitudinal strain; speckle-tracking echocardiography; three-dimensional echocardiography
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Introduction

The incidence and prevalence of heart failure (HF) has increased in recent years and remains a serious medical problem, especially in developed countries [1]. Although recently there have been significant improvements in the medical treatment of HF [2], it is still a major cause of mortality and morbidity. There are increasing data showing a relationship between vitamin D deficiency and the development and progression of HF. Subjects with hypovitaminosis D have greater deterioration in myocardial function than subjects who have sufficient vitamin D [3]. Observational data supports the belief that patients with HF often exhibit vitamin D deficiency [4–8], and higher vitamin D was associated with better outcomes [9, 10].

Considering that the prevalence of vitamin D deficiency varies from 30% to 50% throughout the world [11], we should attempt to understand the pathways involved in the relationship between hypovitaminosis D and cardiovascular health. Although studies have shown a higher prevalence of vitamin D deficiency in patients with HF, it remains unclear whether hypovitaminosis D is a cause or a result of HF. HF patients may be homebound and have reduced exposure to ultraviolet B (UVB) rays, resulting in decreased production of vitamin D [12]. Moreover, recent studies reported conflicting data about the effect of vitamin D on myocardial deformation parameters, which are sensitive indicators of cardiac function [13, 14]. We performed this study to investigate whether vitamin D deficiency affects left ventricular (LV) function even if overt

HF is not present. We hypothesized that myocardial function is compromised in a healthy population with vitamin D deficiency.

Material and methods

Study Population

This single center, cross-sectional study was carried out from the summer term of 2014 to that of 2016 on staff volunteers in clinics and outpatient clinics at Ankara University School of Medicine in the Cardiology and Endocrinology Departments. 120 healthy volunteers, who had no history of coronary artery disease (CAD), and who had no symptoms related with CAD or risk factors leading to CAD, were enrolled in the study. Individuals who smoked were not included. A detailed medical history was taken, and the electrocardiogram was evaluated on admission to the study.

All subjects underwent two-dimensional (2D) and three-dimensional (3D) transthoracic echocardiography (TTE). Seven patients whose echocardiographic images were of poor quality and not appropriate for strain analysis were excluded from the study. Strain analyzes were performed by speckle tracking echocardiography (STE). The study was approved by the local Ethics Committee (decision number: 04-127-14; decision date: 10/03/2014), and it was performed in accordance with the principles outlined in the Declaration of Helsinki.

Laboratory analyses

Plasma glucose, creatinine, calcium, phosphorus, parathyroid hormone, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin, and 25-hydroxy-vitamin D (25-OHD) concentrations were measured in fasting venous blood samples at the same laboratory. Serum 25-OHD was measured with an enzyme immunoassay (ELISA, IDS, Tyne and Wear, UK), 25-OHD ≤ 20 ng/ml was accepted as vitamin D deficiency [15].

Conventional echocardiographic analysis

All subjects underwent a transthoracic echocardiographic examination using a GE VIVID E9 XDClear ultrasound machine (GE, Horten, Norway) with a 3.5-MHz 2D transducer. Standard apical two- and four-chamber views and parasternal long- and short-axis views were obtained. The LV ejection fraction (EF) was calculated by the modified Simpson's method using LV end-diastolic and end-systolic volumes obtained on apical four-chamber views. The left atrial (LA) diameter and LV dimensions at end-systole (LVESD) and end-diastole (LVEDD) were measured in the parasternal long-axis view via M-mode echocardiography [16]. Also, the LV mass index (LVMI) was calculated by the Devereux formula [17].

2D and 3D speckle tracking echocardiographic strain analyses

A cardiologist, blinded to the 25-OHD of each subject, performed 2D global longitudinal strain (GLS) echocardiography images from the apical four-, three-, and two-chamber views of LV from the apex obtained at a rate of 60–80 frames/s [18]. Three consecutive cardiac cycles were recorded for each view, and all data were exported to a workstation (GE, Echo PAC PC Workstation, Version 6.3, Waukesha, Wisconsin, USA) equipped with software for further, offline analysis. Standard, 2D grayscale images were used by the system. The LV endocardial surface was manually outlined on the end-systolic frame, and the software determined the epicardial borders automatically. After the endocardial and epicardial contours had been determined, the left ventricle was divided into six segments in each view. The software then assessed the image quality to determine whether it was suitable for tracking. Sufficient tracking segments were read by the software, and insufficient tracking segments were automatically excluded for each patient. These were corrected manually by the researcher. The value of the 2D LV-GLS was obtained from the average of the 17 segmental, peak systolic, longitudinal strain values on the three apical views (Figure 1).

Three-dimensional, full-volume, LV data were obtained via VIVID E9 XDClear (GE, Horten, Norway) with a 3D transducer. To begin, the 3D full-volume data sets of the LV function were transferred to a workstation. These images were then assessed using a 3D speckle tracking software system that was offline on the workstation (4D LV Quantification, Echo PAC PC, Version 6.3, GE Ultrasound, Waukesha, Wisconsin, USA). Subsequently, end-diastolic two-, three-, and four-chamber views were automatically displayed by the software. The point of the apex and the middle point of the mitral annular line were selected in non-foreshortened, apical views. If necessary, these cut-planes were then manually adjusted to optimize the views. Completion of this step triggered a semi-automated border detection algorithm, which generated end-diastolic and end-systolic LV contours in each of the above cut-planes and in the short-axis view. The software was, therefore, able to reconstruct the 3D endocardial border and determine the epicardial surface. If necessary, the endocardial and epicardial contours were corrected manually. Seven subjects for whom tracking was not found to be adequate were excluded from the analysis. The same procedure was repeated on the end-systolic frame. Following this, 3D speckle tracking analysis was performed by the software throughout the cardiac cycle, dividing the LV measurements into 17 segments according to standard segmentation schemes. Peak GLS measurements were obtained automatically (Figure 2).

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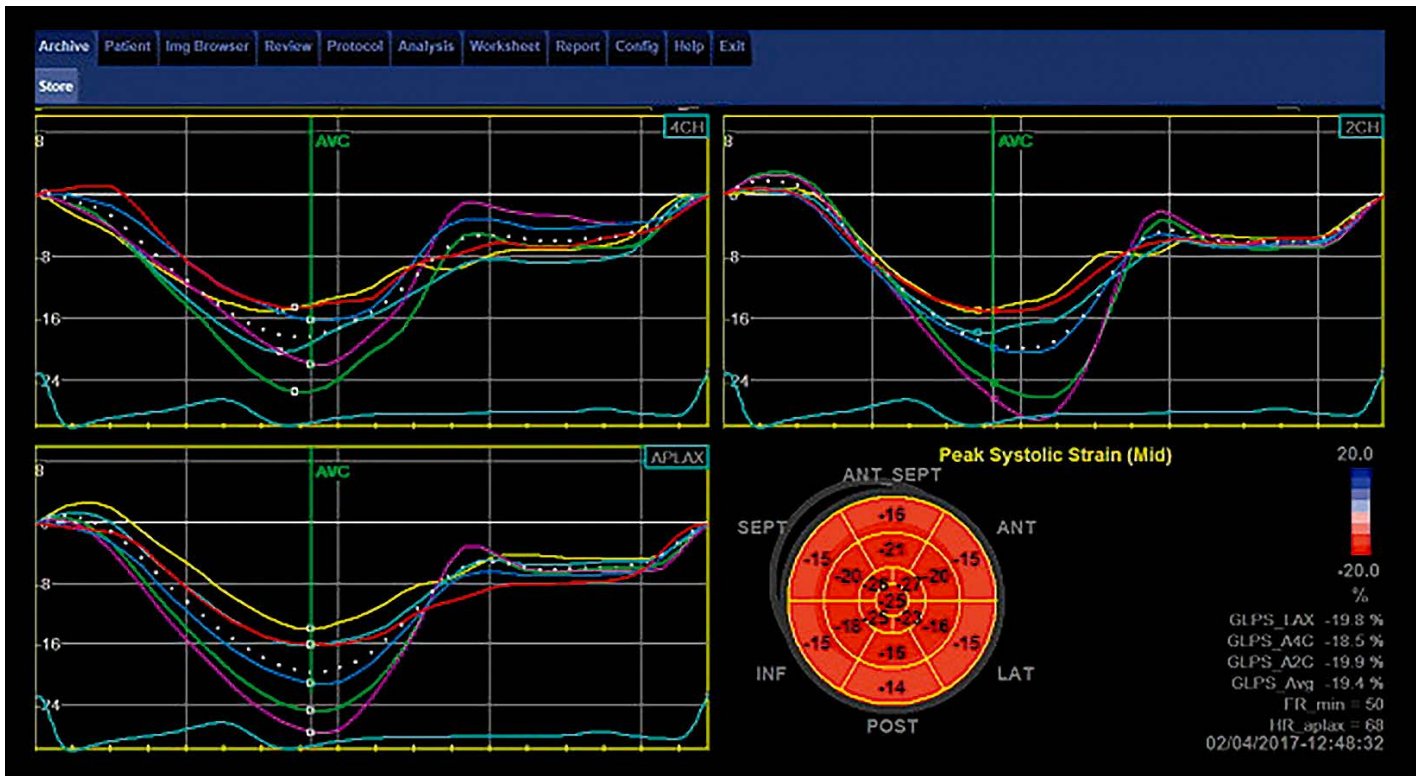
Figure 1. Assessment of left ventricular systolic function using two-dimensional speckle-tracking echocardiography, measurement of global longitudinal strain, and bulls-eye image of the left ventricle



Statistical analyses

Statistical analyses were performed by SPSS 25.0 (Statistical Package for Social Sciences) software. Categorical variables are reported as percentages, and continuous data are reported as mean±standard deviation (SD). Categorical variables were compared using Fisher's exact test and the chi-squared test (χ^2test). Normally distributed data are expressed as mean± SD and were compared using Student's t test for independent groups. Data not normally distributed were expressed as the median (interquartile range (IQR)) in addition to the mean±SD and were compared with the Mann-Whitney U test. Linear relationships between continuous

Figure 2. Illustration of three-dimensional global longitudinal strain analysis

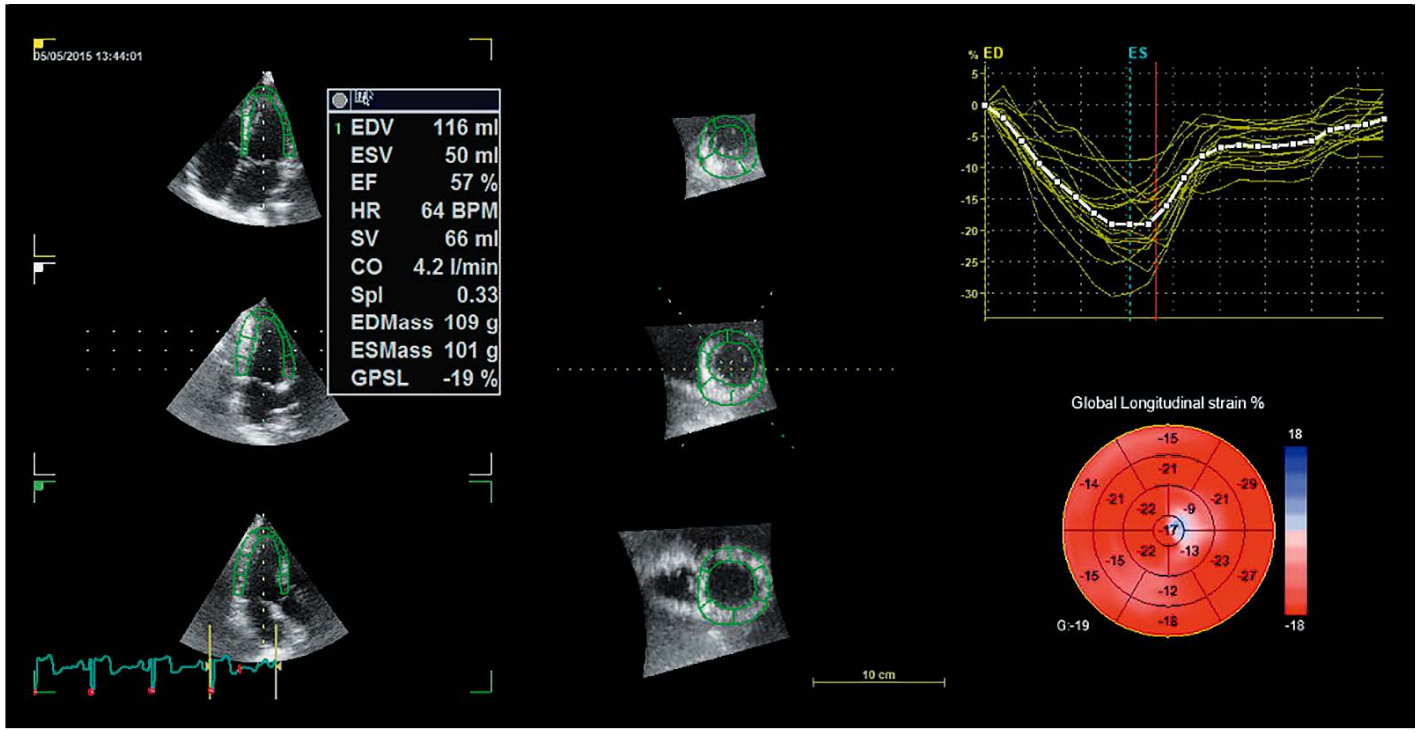


Table 1. Baseline demographic, clinical, and laboratory characteristics of the study population

Variable	Vitamin D deficiency. Absent (n=52)	Vitamin D deficiency. Present (n=61)	p
Age, yrs	43.3±7.7	44.3±6.6	0.555
Female	15 (68.2)	34 (%55.7)	0.309
SBP, mmHg	115.4±11.2	110.3±12.4	0.228
DBP, mmHg	77.3±9.9	76.6±9.5	0.337
BMI, kg/m2	27.2±4.4	26.8±3.7	0.715
Fasting blood glucose, mg/dl	87.1±8.4	88.9±10.7	0.484
Serum creatinine, mg/dl	0.7±0.1	0.82±0.2	0.277
Serum calcium, mg/dl	9.27±0.28	9.18±0.33	0.185
Serum phosphorus, mg/dl	3.71±0.52	3.65±0.68	0.156
Parathyroid hormone, μIU/ml	56.13±23.4	59.21±18.6	0.095
Total cholesterol, mg/dl	204.0±40.3	210.1±41.0	0.554
HDL, mg/dl	49.6±13.0	47.7±13.9	0.376
LDL, mg/dl	109±21.2	115±23.5	0.489
Hemoglobin, g/dl	14.34±1.4	14.33±1.4	0.988

Data are number (%) or mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Conventional and strain echocardiographic findings of patients with and without vitamin D deficiency

Variable	Vitamin D deficiency. Absent (n=52)	Vitamin D deficiency. Present (n=61)	p
EF (%)	60±5.6	59±4.5	0.193
LVEDD, cm	4.65±0.45	4.64±0.48	0.884
LVESD, cm	3.28±0.56	3.21±0.61	0.271
LVMI (g/m^2)	81±12.3	83±10.2	0.102
LA diameter, cm	3.65±0.41	3.67±0.38	0.355
LAVi (ml/m^2)	25.1±3.4	24.8±3.0	0.557
E	0.71±0.15	0.73±0.11	0.219
A	0.59±0.30	0.58±0.29	0.345
DT	185±22	179±25	0.233
E/E'	5.1±2.0	6.2±1.7	0.180
2D GLS	-19.3±4.2 -19.1 (-17.7/-24.1)*	-16.1±3.4 -16.3 (-15.2/-19.9)*	0.001
3D GLS	-24.1±6.9 - 23.7 (-19.3/-27.4)*	-18.3± 5.2 -18.8 (-14.5/22.1)*	0.001

Data are mean±SD and *median (IQR). EF, ejection fraction; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVMI, left ventricular mass index; LA, left atrium; LAVi, left atrial volume index; DT, deceleration time; 2D GLS, two-dimensional global longitudinal strain; 3D GLS, three-dimensional global longitudinal strain.

variables, which were shown to have normal distributions via the one-sample Kolmogorov–Smirnov test, were analyzed by Pearson's correlation test. Pearson's or Spearman's correlation analysis was also performed to explore relationships between vitamin D concentrations and myocardial deformation parameters. Furthermore, linear regression analyses were performed to determine the predictors of LV GLS, the dependent variable. A p value <0.05 was considered statistically significant. Intra-observer reproducibility and calculated intra-class correlation coefficients were evaluated. The intraclass correlation coefficient was 0.98 (95% confidence interval (CI) 0.96–0.99) for intra-observer agreement, and 0.96 (95% CI 0.95–0.98) for interobserver variability. The intra-observer and inter-observer variabilities were 5% and 7%, respectively.

Results

All subjects were categorized into two groups according to their plasma vitamin D concentrations. Subjects with vitamin D less than 20 ng/ml were considered to have vitamin D deficiency [15]. Higher values were accepted as normal vitamin D concentrations. Vitamin D deficiency was detected in 61 subjects included in the study. The baseline demographic, clinical, echocardiographic, and laboratory characteristics of the study population are shown in Tables 1 and 2. There were no significant differences between the two groups in terms of age, sex, body-mass index (BMI), echocardiographic parameters, including LV end-diastolic diameter, LV end-systolic diameter, LA diameter, EF, LVMI, and laboratory parameters, including hemoglobin, fasting blood glucose, serum creatinine, serum calcium, serum phosphorus, parathyroid hormone, total cholesterol, HDL cholesterol, and LDL cholesterol.

Both the 2D and 3D GLS values were lower (mathematically, less negative) in the group with vitamin D deficiency than the subjects with normal vitamin D status (–16.1±3.4 vs –19.3±4.2, p<0.001; –18.3±5.2 vs –24.1±6.9, p<0.001 respectively) (Table 2). Also, vitamin D concentrations were positively correlated with LV GLS (2D GLS for r=0.765 and 3D GLS for r=0.628, p<0.001) (Figures 3 and 4).

Discussion

This study investigated the effects of vitamin D deficiency on LV function in healthy people. Even though our subjects had normal cardiac function on TTE, we assessed myocardial deformation parameters using 2D STE analysis and 3D strain analysis. The results demonstrated that LV GLS was lower in subjects with vitamin D deficiency than in subjects who had normal vitamin D levels, although baseline demographic, clinical, echocardiographic, and laboratory characteristics were similar between these two groups. In addition, we demonstrated that vitamin D concentrations were significantly correlated with both 2D and 3D LV GLS. To the best of our knowledge, this is the first study to evaluate the association of vitamin D deficiency with longitudinal LV systolic function,

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using analysis of 2D and 3D strain in normal, healthy individuals.

In the past decade, there has been growing evidence of a relationship between hypovitaminosis D and poor outcomes in HF [19–23]. An epidemiological study in the United States that included 8,351 people demonstrated that 25-OHD was significantly lower in patients with self-reported HF [24]. Wang et al. [25] reported that, even in individuals who had no previous cardiovascular disease, the rates of myocardial infarction, ischemia, stroke, and HF were nearly 50% higher if 25-OHD was <15 ng/ml. Although the exact mechanism is unclear, there are some potential pathophysiological pathways that could explain the link between vitamin D and HF. Vitamin D can suppress renin transcription and therefore inhibit water and salt retention in HF patients [26]. Vitamin D influences myocardial contractile function by increasing calcium influx and by activating adenylate cyclase in the cardiomyocytes [27, 28]. Parathyroid hormone increases during hypovitaminosis D, and this leads to myocardial fibrosis, increased LV mass, and decreased systolic function [29, 30]. Also, vitamin D deficiency increases matrix metalloproteinases and promotes myocardial fibrosis [31–33].

Figure 3. Correlation between 2D GLS and vitamin D (r=0.765, p<0.001)

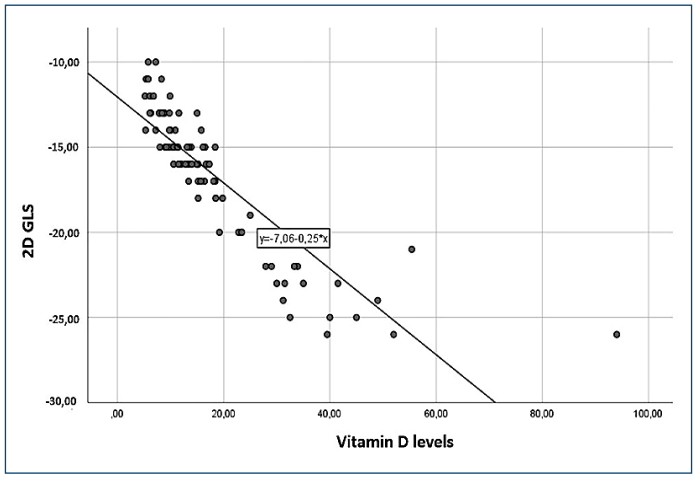
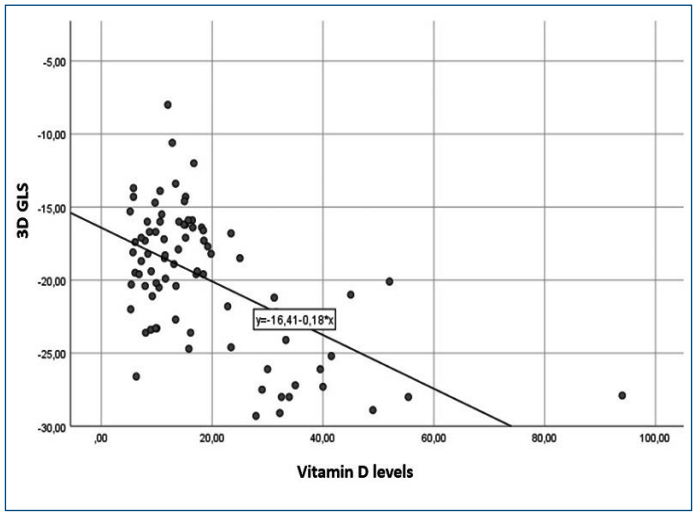


Figure 4. Correlation between 3D GLS and vitamin D (r=0.628, p<0.001)



Thus, whether hypovitaminosis D can lead to subclinical myocardial dysfunction is a new field of research. With the development of echocardiographic techniques, deformation parameters are among the most used to measure to evaluate LV function. Although routine transthoracic echocardiography is a useful method for the evaluation of cardiac disease, it is not sufficiently sensitive for detecting subclinical myocardial dysfunction. Therefore, we used 2D and 3D strain analysis, which have been shown to be effective for early detection of deteriorated LV systolic function [18, 34–36].

Furthermore, 3D strain analysis has some advantages over 2D strain. Due to the spatial orientations of LV myocytes, they contract multidirectionally. Thus, 3D imaging can more accurately assess LV function [37]. Also, the 3D mode avoids the foreshortenings of apical view and analyzes the whole ventricle from one data set. This reduces the time required for the analysis. It can display motion of speckles in all three dimensions, and this helps to resolve the problem of out-of-plane motion encountered in 2D STE [38].

Previous studies of cardiac function in subjects with vitamin D deficiency have usually used conventional echocardiographic measurements such as LVMI, and some assessed myocardial deformation parameters [13, 14, 39–42]. From a similar investigation, Omidi et al. [14] reported contradictory findings. In a cross-sectional study, they evaluated 45 subjects with vitamin D deficiency and 53 subjects with normal vitamin D, all of whom were nondiabetic and had undergone angiographic evaluation showing no significant CAD. Omidi et al found no difference in myocardial deformation parameters evaluated by 2D STE between the subjects with vitamin D deficiency and those without. We found that poor vitamin D status was related with impaired LV GLS evaluated by 2D and 3D STE. The difference between the results of our study and that study might be explained by differences in the study population. In the current study, only healthy subjects with no risk factors for CAD were included. In the study of Omidi et al., patients who needed coronary angiography due to signs or symptoms of CAD were enrolled. In addition, Omidi et al. evaluated myocardial deformation only by 2D STE. Our use of 3D strain, which is superior to 2D STE [37, 38], likely contributed further to the positive findings of the current study.

In another similar study, Sunbul et al. [13] investigated the effect of vitamin D deficiency and its supplementation on myocardial deformation parameters of 50 patients with hypovitaminosis D, who were free of cardiovascular risks. Sunbul et al. reported that patients with impaired LV GLS had significantly lower vitamin D than patients with normal LV GLS analyzed by 2D STE. In that study,

the relationship between vitamin D and LV GLS was similar to that of our study. Sunbul et al. also evaluated the effects of three months of vitamin D supplementation on myocardial deformation parameters. They observed improvement in LV GLS in parallel with the increase of vitamin D. Consequently, it has been suggested previously that vitamin D supplementation may have beneficial effects on myocardial strain. Although the design of that study was different, and only 2D analysis was used, the results were in parallel with those of our study.

Özer et al. [39] investigated LV function in diabetic and nondiabetic patients with vitamin D deficiency and found that 2D GLS was impaired in those with vitamin D deficiency [39]. In another study in patients with vitamin D deficiency; Khaleghi et al. evaluated the relationship between vitamin D deficiency and 2D LA strain and showed that left atrial functions were not impaired in those with vitamin D deficiency [40].

Pishgahi et al. evaluated vitamin D and TDI echocardiography parameters in patients with thalassemia major and showed that vitamin D deficiency was associated with systolic dysfunction in these patients [41]. Using more conventional echocardiographic parameters, Patange et al. found in 34 children with chronic kidney disease, who had no history of heart disease, that increased LVMI was negatively correlated with 25-OHD [42]. Also, in that study, low vitamin D concentrations and systolic hypertension were shown to be the only independent predictors of LVMI in children with chronic kidney disease. In our study, the LVMI of the two groups were compared to rule out the possible effect on GLS, and there was no statistically significant difference between the groups.

To summarize, our study has important clinical implications for subjects with vitamin D deficiency. The results demonstrated that clinicians should pay more attention to evaluating patients with vitamin D deficiency due to its subclinical effects on cardiovascular function.

Limitations of the study

The number of patients in this study was small. Therefore, large, randomized, controlled trials are needed. Also, we did not measure renin-angiotensin-aldosterone system markers or inflammatory cytokines and matrix metalloproteinases, all of which can play roles in the development of LV systolic dysfunction. Coronary angiography was not performed to definitely exclude CAD. Cardiac magnetic resonance imaging (MRI) was not performed to evaluate the presence of myocardial fibrosis. The lack of long-term patient follow-up is another limitation.

Conclusion

Individuals with vitamin D deficiency had lower 2D and 3D GLS values than individuals with normal vitamin D. More attention should be paid to healthy subjects with vitamin D deficiency because of its potentially negative effect on cardiac function.

No conflict of interest is reported.

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