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Left and right ventricular function by echocardiography, tissue doppler imaging, carotid intima media thickness, and asymmetric dimethylarginine levels in female adolescents with vitamin D deficiency

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Abstract

Background: The aim of our study was to assess left and right ventricle systolic and diastolic functions in female adolescents with vitamin D deficiency using conventional echocardiography and pulsed-wave tissue Doppler imaging and to investigate carotid intima media thickness and asymmetric dimethylarginine levels. *Methods:* Sixty-six female adolescents were enrolled in this study. The female adolescents were divided into a vitamin D deficiency group (n: 34) and a control group (n: 32). All subjects underwent laboratory blood tests, including asymmetric dimethyl arginine, complete two-dimensional, pulse, and tissue Doppler echocardiography, and measurement of the carotid intima-media thickness. *Results:* The vitamin D-deficient female adolescent group had normal left and right ventricle systolic and diastolic functions and normal global systolic and diastolic myocardial performance. In the patients with vitamin D deficiency, the carotid intima-media thickness was higher than that in the controls. In the patients within the vitamin D deficiency group, vitamin D was found to be positively correlated with magnesium and negatively correlated with phosphorus and left atrial dimension. *Conclusions:* The results of this study demonstrate that vitamin D deficiency in female adolescence is associated with normal myocardial geometry and function. Although it has been associated with normal levels of asymmetric dimethyl arginine concentration, high measured carotid intima-media thickness may reflect endothelial dysfunction.

Vitamin D plays a crucial role in maintaining bone health, principally via its effects on calcium metabolism. A growing body of evidence has suggested that vitamin D may also play a role in the regulation of the function of various organs and tissues, especially in the heart, kidneys, brain, and muscles.[1] In the cardiovascular system, vitamin D receptors have been found in both endothelial and myocardial cells.[2] Mice with a systemic knockout of the vitamin D receptor developed cardiac hypertrophy by differentiation and proliferation of cardiomyocytes and activation of the cardiac renin–angiotensin system, which leads to hypertension, coronary artery disease, left ventricular hypertrophy, and congestive heart failure.[3]

Nitric oxide is the main vasorelaxing and antithrombotic factor produced by endothelial cells through the action of endothelial nitric oxide synthase. Asymmetric dimethylarginine is the major endogenous inhibitor of nitric oxide synthase, leading to endothelial dysfunction and atherosclerotic vascular disease.[4] The increase in plasma asymmetric dimethylarginine concentrations occurs mainly following inhibition of dimethylarginine dimethylaminohydrolase, the enzyme responsible for the catabolism of asymmetric dimethylarginine.[5] Vitamin D deficiency may adversely affect endothelial function and structure, leading to increased aortic stiffness[6] and high carotid intima media thickness measurement which are known to be associated with atherosclerosis.

The aim of our study was to assess left and right ventricle systolic and diastolic functions in female adolescents with vitamin D deficiency using conventional echocardiography and pulsed-wave tissue Doppler imaging and to investigate asymmetric dimethylarginine levels. We also studied left and right ventricle structural remodelling as well as carotid intima media thickness in female adolescents with vitamin D deficiency.

Materials and methods

Thirty-two female adolescents (mean age 13.9 ± 1.8 years, range 10–17; mean body mass index [BMI] 19.3 ± 2.9 kg/m2) were recruited from vitamin D deficiency admitted to the paediatric endocrinology unit between June 2013 and June 2014. Control participants (mean age 14.1 ± 1.2 years, range 12–16; mean BMI 19.1 ± 1.7 kg/m2) were selected from healthy female adolescents who attended the hospital for minor illnesses, such as the common cold, conjunctivitis, short stature, and constipation.

Patients with clinical or laboratory signs of any systemic disease, including hepatic disease, renal disease, or a malabsorptive disorder, disorder of bone or calcium metabolism, use of an anticonvulsant or systemic glucocorticoid, and use of a vitamin D supplement, were excluded. Obesity causes low serum vitamin D levels due to the high storage capacity of vitamin D in adipose tissue. At the same time, obesity is a cardiovascular risk factor as a component of metabolic syndrome, so we included only nonobese participants in our study. The study protocols were approved by our hospital's ethics committee (approval number 0.28.00.00/130-330). Signed informed consent forms were obtained from the parents of the adolescents.

Height and weight were measured with an empty bladder in postabsorptive conditions. BMI was calculated as weight in kilograms divided by the square of height in metres. Waist circumference was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration. Hip circumference was measured over the great trochanters. The pubertal developmental stage was assessed by a single paediatric endocrinologist using the Tanner criteria. Staging for sexual maturation was > 2 in all patients (Tanner stages II–IV). After resting for ≥ 5 minutes, systolic and diastolic blood pressures were measured in the sitting position, using a mercury-gravity manometer and a cuff appropriate for body size.

Fasting blood samples (at 8 A.M.) were obtained to measure serum glucose insulin levels and other parameters in the morning by venipuncture after an overnight fast (≥ 12 hours). Serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using routine enzymatic methods with an Abbott Diagnostics c16000 chemistry analyzer (Abbott Diagnostics, Lake Forest, Illinois). Serum insulin levels were measured using the IMMULITE immunoassay (Siemens Healthcare Diagnostics, Camberley, United Kingdom). Insulin resistance was estimated using homeostasis model assessment of insulin resistance (fasting insulin concentration [mU/ml] X fasting glucose concentration [mmol/L]/22.5).[7]

Measurement of Asymmetric dimethylarginine (ADMA) levels was accomplished by high-performance liquid chromotography, using the method described by Chen[8] with minor modifications. Serum 25-hydroxyvitamin D levels were measured using chemiluminescent microparticle immunoassay (CMIA) methods with an Abbott Architect i2000 SR (Abbott Diagnostics, Abbott Park, IL). Vitamin D deficiency was defined as 25-hydroxyvitamin D concentration < 20 ng/ml[9] then, we considered our patients as vitamin D deficiency when having serum 25-hydroxyvitamin D level lower than < 20 ng/ml. Vitamin D level was > 20 ng/ml in all control participants.

Carotid ultrasound studies were performed by a single radiologist, who was blinded to the clinical and laboratory status of the patients, using high-resolution B-mode ultrasonography (Logiq 7) using a high-resolution linear-array vascular transducer (14 MHz). An optimal 2-dimensional image of the common carotid artery was obtained in which the near and far wall intima-media complex was well visualised. After a 10-minute rest and according to standard guidelines, the M-mode cursor was then placed 1 cm proximal to the beginning of the carotid artery bulb during end-diastole. Carotid intima-media thickness was calculated by taking the mean value of 3 measurements. There was no evidence of carotid plaque formation in all the obese and control groups.

All echocardiographic and Doppler examinations were performed by a single expert paediatric cardiologist, who was blinded to the clinical and laboratory results of the study group. ProSound Alpha 7 (Aloka, Hitachi-Aloka Medical, Tokyo, Japan) with a 3-MHz phased-array transducer was used for each study subject. Conventional echocardiographic evaluation from the parasternal long-axis view included left ventricle end-diastolic and end-systolic diameter, septal and left ventricle posterior wall thicknesses in diastole and systole, right ventricle free wall thicknesses in diastole and systole, the left ventricle ejection fraction, and left ventricle fractional shortening. Teichholz's M-mode formula was used to calculate the left ventricle ejection fraction and left ventricle fractional shortening. All data were determined according to the recommendations of the American Society of Echocardiography.[10] Relative posterior wall thicknesses was calculated as (interventricular septal thickness in diastole + left ventricle posterior wall thickness in diastole)/ left ventricle end-diastolic diameter. Left ventricular mass was calculated using the Devereux[11] formula and indexed to height$^{2.7}$.

Transmitral and transtricuspid flow patterns were obtained by pulsed-wave Doppler echocardiography from the apical 4-chamber view with the sample volume placed at the mitral and tricuspid valves leaflets tips. Peak early (Em, Et) and late (Am, At) diastolic velocities, the (E/A)m and (E/A)t ratios, isovolumetric relaxation times, isovolumetric contraction times, and ejection times were measured. The Doppler-derived index of combined systolic and diastolic myocardial performances (Tei index; [isovolumetric relaxation time + isovolumetric contraction time]/ejection time) was used to quantify global left and right ventricles function.[12]

A 5-mm pulsed-wave Doppler tracing was placed at the septal and lateral segments of the mitral valve, and lateral segment of the tricuspid valve and peak myocardial systolic (sm, st), early (e'm, e't), and late diastolic (a'm, a't) velocities were measured from the apical 4-chamber view. (E/e')m and (E/e')t ratios of the left ventricle and the right ventricle were determined by using previously estimated Doppler values.

The left ventricle and right ventricle Tei index was calculated according to the formula: (Isovolumic relaxation time+ Isovolumic contarction time)/Ejection time.

Right ventricle global systolic function was assessed as the tricuspid annular plane systolic excursion, which was measured as the difference between the distance among the tricuspid annulus and right ventricle apex end-diastole and end-systole of the same cardiac cycle.[13]

Statistical analysis

Continuous variables are expressed as mean ± SD (range). Normality assumptions were assessed before conducting parametric tests. When all groups were compared for parameters,

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analyses of variance were used; post hoc analysis was performed using Tukey's honestly significantly different test. Bivariate associations of continuous variables were assessed using Pearson's correlation coefficients. A p value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois).

Results

We studied 66 healthy female adolescents; the vitamin D deficiency group included 32 adolescents (age 13.9 ± 1.8 years), while the remaining 34 female adolescents (age 14.1 ± 1.2 years) were in the control group. Demographic characteristics and cardiometabolic risk factors for the study participants are shown in Table 1.

Heart rate was significantly higher in the controls than in the vitamin D deficiency patients. There were no significant differences between the groups regarding age, body weight, height, BMI, waist and hip circumferences, systolic blood pressure, and diastolic blood pressure. There were no significant differences in TC, Low-density lipoprotein (LDL), and High-density lipoprotein (HDL) cholesterol levels, whereas Trigliseride (TG) levels were significantly higher in the vitamin D deficiency group than in the controls. We also found that there were significantly higher serum insulin and HOMA-IR levels in the vitamin D deficiency group than in the controls. Additionally, asymmetric dimethyl arginine levels were nonsignificantly higher in the vitamin D deficiency group than in the controls. In the vitamin D deficiency group, calcium, phosphate, alkaline phosphatase, magnesium, and parathormone were within normal levels. However, vitamin D levels were low (7.7 ± 3.4 ng/ml (3–16)) in the study group.

Conventional echocardiographic (2-dimensional, M-mode, and pulsed-wave Doppler) findings and carotid intima-media thickness results of the patients and controls are listed in Table 2.

No significant differences were found in the left ventricular diameter at end systole and end diastole, interventricular septal thickness at end systole, left ventricular posterior wall thickness at end diastole, or right ventricular free wall thickness at end systole and diastole in either group, but there was significantly increased left ventricular posterior wall thickness at end systole in controls compared with the vitamin D deficiency group ($p = 0.002$). By conventional echocardiography, the left ventricle ejection fraction, left ventricle shortening fraction, and left ventricle mass were similar in the vitamin D deficiency and control groups. The left atrial and aortic diameters were also similar in both the groups.

Tricuspid annular plane systolic excursion was completely preserved in both groups. The vitamin D deficiency group had significantly higher carotid intima-media thickness than the controls ($p = < 0.0001$).

The parameters of left ventricle myocardial systolic function obtained by tissue Doppler (s'_{septal} and $s'_{lateral}$) seemed normal in the left ventricle interventricular septum and lateral wall in both groups. The parameters of left ventricle diastolic function, such as E/A_{mitral}, E/e'_{septal} and $E/e'_{lateral}$ values, were similar in both groups. The left ventricle Tei indexes, which indicate damage to left ventricle global function, were also similar in the vitamin D deficiency group and controls.

The parameters of the right ventricle myocardial systolic function obtained by tissue Doppler ($s'_{tricuspid}$) seemed normal in the right ventricle interventricular septum and lateral wall in both groups. Additionally, the parameters of right ventricle diastolic function, such as $E/A_{tricuspid}$ and $E/e'_{tricuspid}$, were similar in the vitamin D deficiency group compared to the controls. Similar to the left ventricle, the Tei index of the right ventricle was normal in both groups (Table 3).

In the vitamin D deficiency group, vitamin D was not correlated with anthropometric measurements or cardiometabolic risk

Table 1. Clinical features of healthy controls and vitamin D deficiency adolescents.

Variable	Controls	D hypovitaminosis	*p* value
Subjects	34	32	
Age (years)	14.1 ± 1.2 (12–16)	13.9 ± 1.8 (10–17)	0.489
BMI (kg/m^2)	19.1 ± 1.7 (16.6–23.5)	19.3 ± 2.9 (14.4–27.3)	0.719
Waist circumference (cm)	71.0 ± 5 (61–84)	69.5 ± 7.7 (56–91)	0.283
Hip circumference (cm)	89.0 ± 4 (78–97)	87.2 ± 8.2 (69–100)	0.132
Waist circumference/ hip circumference ratio	0.79 ± 0.06 (0.67–0.93)	0.80 ± 0.07 (0.65–0.99)	0.831
Systolic BP (mm Hg)	102.0 ± 8.6 (80–110)	103.9 ± 11.6 (80–120)	0.493
Diastolic BP (mm Hg)	63.0 ± 6.9 (40–70)	64.0 ± 8.1 (50–85)	0.819
Heart rate (beats/min)	92 (17)	88 (18)	0.021 *
Total cholesterol (mg/dl)	148 ± 24 (104–194)	156 ± 26.3 (99–214)	0.246
Triglyserides (mg/dl)	65 (26)	84 (51)	0.010 *
Low-density lipoprotein cholesterol (mg/dl)	83 ± 20 (38–117)	87 ± 23 (55–147)	0.556
High-density lipoprotein cholesterol (mg/dl)	52 ± 8 (41–70)	49 ± 11 (33–79)	0.177
Fasting glucose (mg/dl)	82.0 ± 4 (73–88)	84.4 ± 7.3 (62–103)	0.105
Fasting insulin (U/ml)	7.1 (3.3)	10.2 (6.1)	< 0.0001 *
HOMA-IR	1.5 ± 0.45 (0.8–2.5)	2.4 ± 1.22 (0.6–5.6)	0.006 *
ADMA	0.27 ± 0.17 (0.10–0.54)	0.46 ± 0.13 (0.34–0.61)	0.129
Calcium (mg/dl)		9.6 ± 0.3 (9.0–10.2)	
Phosphorus (mg/dl)		4.2 ± 0.8 (2.4–6.4)	
Magnesium (mg/dl)		2.2 ± 0.6 (1.9–4.4)	
Alkaline phosphatase (mg/dl)		177.9 ± 94.4 (46–373)	
D vitamine		7.7 ± 3.4 (3–16)	
Parathormone (pg/ml)		55.8 ± 40.7 (11–203)	

*$p < 0.05$, controls versus hypovitaminosis subjects.

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Table 2. Conventional echocardiographic findings and carotit intima-media thickness measurements in controls and vitamin D deficiency adolescents.

	Controls (n = 34)	D Hypovitaminosis (n = 32)	p value
Left Ventricle			
LV end-diastolic diameter (mm)	42.2 ± 2.9 (37–49)	41.8 ± 3.5 (33–50)	0.651
LV end-systolic diameter (mm)	26.6 ± 2.3 (22–32)	25.8 ± 3.1 (20–31)	0.223
Interventricular septal diameter in diastole (mm)	7.0 (0)	7.0 (0)	0.007*
Interventricular septal diameter in systole (mm)	8.1 ± 1.1 (7–12)	8.1 ± 1.3 (6–11)	0.971
LV posterior wall diameter in diastole (mm)	6.7 ± 0.7 (5–8)	6.4 ± 0.8 (5–8)	
LV posterior wall diameter in systole (mm)	11.0 (2)	10.0 (2)	0.002*
LV ejection fraction (%)	67 ± 2.8 (62–72)	68 ± 4.2 (60–77)	0.078
LV fractional shortening (%)	36 ± 2.4 (32–41)	37 ± 3.4 (31–45)	0.068
Relative wall thickness (mm)	3.31 ± 0.24 (2.70)	3.19 ± 0.33 (2.70)	0.115
LV mass (g)	93 ± 16.1 (58)	90 ± 23.1 (51)	0.565
LV mass index (g/m^2)	27 ± 4.2 (18)	29±7.1 (18)	0.249
Left atrium			
Left atrial dimension (mm)	24 ± 2.2 (20–28)	24 ± 2.6 (18–28)	0.958
Aortic dimension (mm)	19 ± 1.6 (16–22)	20 ± 2.9 (16–26)	0.052
Right ventricle			
RV free wall diameter in diastole (mm)	4.0 ± 0.49 (3–5)	3.7 ± 0.88 (2–6)	0.685
RV free wall diameter in systole (mm)	5.2 ± 0.62 (4–6)	5.2 ± 0.96 (4–7)	0.203
Tricuspid annular plane systolic excursion (mm)	22.7 ± 1.8 (18–29)	23.6 ± 2.9 (20–33)	0.173
Carotis intima media thickness (mm)	0.368 ± 0.024 (0.33–0.45)	0.401 ± 0.030 (0.34–0.44)	<0.0001*

*p < 0.05, controls versus hypovitaminosis subjects.

Table 3. Comparison of left and right ventricular systolic and diastolic functions by pulse wave doppler and tissue doppler imaging measurements in controls and vitamin D deficiency adeolescents.

	Controls (n = 34)	D Hypovitaminosis (n = 32)	p value
Left ventricle			
Mitral peak early diastolic wave (E) (m/s)	0.93 ± 0.13 (0.62–1.12)	0.91 ± 0.11 (0.75–1.10)	0.375
Mitral peak late diastolic wave (A) (m/s)	0.55 ± 0.11 (0.38–0.75)	0.53 ± 0.09 (0.40–0.80)	0.661
Mitral peak early diastolic wave/ peak late diastolic wave ratio $(E/A)_{mitral}$	1.74 ± 0.29 (1.27)	1.71 ± 0.31 (1.25)	0.677
Septum peak myocardial systolic velocity (s'_{septal}) (cm/s)	10.6 ± 1.5 (7.8)	10.8 ± 2.1 (8.0)	0.880
Septum peak myocardial early diastolic velocity (e'_{septal}) (cm/s)	15.8 ± 2.1 (5.6	16.3 ± 2.4 (10.0	0.889
Lateral peak myocardial systolic velocity $(s'_{lateral})$ (cm/s)	11.4 ± 2.0 (7.6)	11.7 ± 2.1 (8.0)	0.827
Lateral peak myocardial early diastolic velocity $(e'_{lateral})$ (cm/s)	19.2 ± 3.2 (11.1)	19.8 ± 2.9 (13.0)	0.275
LV global performance index	0.537 ± 0.080 (0.32)	0.532 ± 0.085 (0.35)	0.793
Right ventricle			
Tricuspid peak early diastolic wave (E) (m/s)	0.65 ± 0.07 (0.50–0.79)	0.63 ± 0.10 (0.43–0.89)	0.448
Tricuspid peak late diastolic wave (A) (m/s)	0.37 ± 0.08 (0.25–0.55)	0.39 ± 0.09 (0.20–0.60)	0.323
Tricuspid peak early diastolic wave/ peak late diastolic wave ratio $(E/A)_{tricuspid}$	1.80 ± 0.35 (1.30)	1.65 ± 0.28 (0.81)	0.553
Tricuspid peak myocardial systolic velocity $(s'_{tricuspid})$ (cm/s)	14.5 ± 1.7 (11.0)	14.6 ± 2.7 (9.0)	0.928
Tricuspid peak myocardial early diastolic velocity $(e'_{tricuspid})$ (cm/s)	17.9 ± 4.4 (13.0)	17.9 ± 3.1 (12.0)	0.980
RV global performance index	0.634 ± 0.09 (0.45)	0.594 ± 0.13 (0.37	0.582

*p < 0.05, controls versus D hypovitaminosis subjects.

parameters, including lipid profile, glucose, and HOMA-IR. We could also not find a correlation between vitamin D and ADMA and Parathormon (PTH) levels. In the vitamin D deficiency group, vitamin D was only positively correlated with magnesium and negatively correlated with phosphorus (Table 4).

In the vitamin D deficiency group, vitamin D was not correlated with global performance indexes or regional tissue Doppler imaging myocardial performance indexes in either the left or right ventricles. We also did not find a correlation between left ventricle mass and carotid intima media thickness. In the vitamin D

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Table 4. Pearson's correlation between vitamin D and clinical and laboratory parameters in vitamin D deficiency adolescents.

Variable	D Hypovitaminosis	
	r	*p* value
Age	–0.332	0.091
BMI	–0.149	0.458
Waist circumference	–0.096	0.648
Hip circumference	–0.052	0.806
Waist circumference/ hip circumference ratio	–0.059	0.779
Systolic BP	0.065	0.764
Diastolic BP	0.194	0.364
Heart rate	0.058	0.798
Fasting glucose	–0.066	0.754
Fasting insulin	–0.142	0.498
HOMA-IR	–0.192	0.369
Total cholesterol	–0.097	0.639
High-density lipoprotein cholesterol	0.004	0.983
Low-density lipoprotein cholesterol	0.018	0.929
Triglyserides	–0.260	0.199
ADMA	–0.565	0.618
Calcium	–0.022	0.927
Magnesium	0.736	0.015*
Phosphorus	–0.479	0.044*
Alcaline Phosphatase	0.217	0.386
Parathormone	–0.178	0.465

*Statistically significant ($p < 0.005$).

Table 5. Pearson's correlation between vitamin D and cardiac geommetry and functions in vitamin D deficiency adolescents.

Variable	D hypovitaminosis	
	r	*p*
Left ventricle		
LV mass (g)	–0.166	0.407
LV mass index (g/m$^{2.7}$)	–0.186	0.353
Left atrial dimension (mm)	–0.402	0.042*
LV ejection fraction (%)	0.002	0.991
Septum peak myocardial systolic velocity (s'$_{septal}$) (cm/s)	–0.042	0.834
Lateral peak myocardial systolic velocity (s'$_{lateral}$) (cm/s)	0.115	0.568
Peak early diastolic velocity/septum peak myocardial early diastolic velocity ratio (E/e' $_{septal}$)	–0.097	0.631
Peak early diastolic velocity/lateral peak myocardial early diastolic velocity ratio (E/e' $_{lateral}$)	0.059	0.776
LV myocardial performance index	0.145	0.471
Right ventricle		
RV free wall diameter in diastole (mm)	0.055	0.789
Tricuspid annular plane systolic excursion (mm)	–0.206	0.304
Tricuspid peak myocardial systolic velocity (s'$_{tricuspid}$) (cm/s)	0.140	0.487
Tricuspid peak early diastolic velocity/peak myocardial early diastolic velocity ratio (E/e'$_{tricuspid}$)	–0.306	0.120
RV myocardial performance index	0.320	0.104
Carotis intima media thickness	–0.296	0.305

*Statistically significant ($p < 0.05$).

deficiency group, vitamin D was negatively correlated with the left atrial dimension. (Table 5)

Discussion

The main role of vitamin D is the maintenance of calcium and phosphorus homeostasis. In the cardiovascular system, vitamin D deficiency also found a risk factor for hypertension, dyslipidaemia, and insulin resistance.

Several mechanisms have been proposed relating vitamin D deficiency to hypertension, such as renin–angiotensin–aldosterone system activation, abnormal nitric oxide regulation, oxidative stress, or altered inflammatory pathways. Animal experiments have shown that vitamin D reduces the activity of the renin–angiotensin–aldosterone system and improves vasorelaxation of blood vessels; therefore, vitamin D deficiency is associated with the risk of hypertension. To reveal the mechanism by which vitamin D regulates the renin–angiotensin–aldosterone system, Li et al[2] analysed vitamin D receptorknockout animals, and Zhou et al[14] analysed 1αhydroxylase geneknockout mice. They reported that the renin gene expressed in the kidney was increased as well as angiotensin II activity in plasma and eventually led to high blood pressure and myocardial hypertrophy.

The results of several observational studies suggest a relationship between the plasma concentration of vitamin D and the risk of arterial hypertension. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study showed that lower vitamin D levels are independently associated with an upregulated circulating renin–angiotensin–aldosterone system.[15] Additionally, Forman et al[16] found in normotensive individuals and Resnick et al[17] found in the patients with essential hypertension that the vitamin D-deficient group had higher plasma angiotensin II levels and renin activity than the normal vitamin D group. Pacifico et al[18] showed that vitamin D deficiency was associated with elevated systolic, diastolic, and mean blood pressures.

Randomied controlled trials showed conflicting results about the effect of vitamin D supplementation on blood pressure. While some studies[19] found that vitamin D supplementation was associated with a significant reduction in diastolic and/or systolic blood pressure, Hauger [20] et al and Wamberg[21] et al reported that vitamin D supplementation did not have a significant effect on blood pressure.

In our study, like Matter et al,[22] there was no significant difference in blood pressure in the vitamin D deficiency group compared to controls. Furthermore, we found no associations among vitamin D levels and systolic and diastolic blood pressures. Although it has been claimed that vitamin D deficiency activates the renin–angiotensin–aldosterone system, in our patients with vitamin D deficiency, blood pressure values have been similar to controls since we included only thin adolescents in our study and excluded secondary causes of hypertension such as drug use, kidney, and thyroid diseases.

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Numerous studies have reported the association between vitamin D levels and lipid panels in children and adolescents with obesity.[23,24] However, Hirschler et al[25] claimed that their findings indicated a relationship between vitamin D levels and the lipid profile, even in nonobese children. They found that vitamin D-deficient children had a higher TG level and TG/HDL-C ratio, whereas HDL-C was significantly and directly associated with vitamin D. Additionally, Jiang et al[26] and Sharba et al[27] found that low vitamin D levels result in lipid abnormalities — that is, an increase in TG, TC, and LDL-C levels and a decrease in HDL-C levels. In contrast, Colak et al[28] found no significant association between any of the variables and vitamin D levels in the lean group. In our study, there were no significant differences in TC, LDL, and HDL cholesterol levels, whereas TG levels were significantly higher in the vitamin D deficiency group than in the controls. In addition, we found no association between vitamin D levels and lipid parameters.

Investigators speculated that vitamin D could affect lipid metabolism either directly or indirectly through alterations in parathyroid hormone and/or calcium concentrations.[29] Low levels of vitamin D led to high parathormone and low serum calcium concentrations. Higher serum concentrations of parathormone are associated with increased lipogenesis and decreasing lipolysis, resulting in a high TG level. Therefore, the presence of high vitamin D and low parathormone levels can reduce TG by increasing lipolytic activity and peripheral removal.[14] Moreover, vitamin D increases intestinal calcium absorption, leading to increased serum calcium concentrations and promoting the conversion of cholesterol into bile acids in the liver, resulting in reduced cholesterol levels.

According to a systematic review and meta-analysis, vitamin D supplementation has no or little beneficial effect on cardiometabolic outcomes in children and adolescents.[20]

There is a growing, largely conflicting literature on the role of vitamin D in the incidence of diabetes, peripheral glucose uptake regulation of pancreatic insulin secretion, and diabetic complications. The exact mechanisms that are involved in terms of the effect of vitamin D on glucose metabolism are unclear. Vitamin D deficiency may contribute to both insulin resistance and the onset of diabetes by excessive Ca2+ and reactive oxygen species signalling that results in β-cell death.[30]

Xiao et al[31] found associations between plasma vitamin D concentrations and cardiometabolic risk factors in their nationwide cross-sectional study. They reported that vitamin D concentration was inversely related to TG, fasting blood glucose, insulin, and HOMA-IR in both genders. Lee et al[24] showed a modest reduction in HOMA-IR but not in fasting blood glucose after vitamin D treatment in individuals with type 2 diabetes. Niroomand et al[32] found lower HOMA-IR in prediabetes patients with vitamin D deficiency that was treated with high-dose vitamin D. They claimed that high vitamin D increases insulin sensitivity and decreases the risk of progression towards diabetes. Sethuraman et al[33] found in their study that in obese participants, who had high baseline HOMA-IR, there was no significant improvement with vitamin D treatment in HOMA-IR values, but vitamin D may contribute to higher fasting insulin, but not insulin sensitivity. Our findings revealed that HOMA-IR and fasting insulin levels were significantly higher in the study group, but fasting blood glucose levels were similar in both groups. Moreover, we found no significant correlation between vitamin D concentrations and HOMA-IR and fasting insulin.

Elevated levels of asymmetric dimethylarginine in plasma cause impaired production of nitric oxide synthesis, leading to endothelial dysfunction and the development of atherosclerotic vascular disease. Some studies have found that vitamin D deficiency may adversely affect endothelial function.[34] The association between vitamin D deficiency and increased aortic stiffness has been demonstrated in healthy subjects.[35] IL-6 is the cytocin involved in the development of inflammation in blood vessels, which leads to atherosclerosis. Bednarek-Skublewska et al[36] found a negative correlation between vitamin D and IL-6 levels. Choi et al.[37] reported that the mean asymmetric dimethylarginine concentration was significantly higher in elderly patients with vitamin D deficiency than in controls. However, we found that asymmetric dimethylarginine levels were higher, but not significantly, in vitamin D-deficient adolescents than in controls. Furthermore, we found no correlation between asymmetric dimethylarginine and vitamin D levels.

The results of studies correlating serum vitamin D levels with markers of subclinical atherosclerosis have been conflicting. Taskiran et al[38] studied type 1 DM, and Monteiro Júnior et al[39] studied healthy individuals and found a possible association between vitamin D and carotid intima media thickness. They reported that there was no association between vitamin D and carotid intima media thickness. In contrast, Aydin et al[40] and Choi et al[37] showed that serum vitamin D levels were negatively associated with carotid intima media thickness. Furthermore, a meta-analysis reported by Chen et al[41] comprehensively revealed a close link between vitamin D deficiency and carotid atherosclerosis. In our study, we found significantly higher carotid intima media thickness in vitamin D-deficient adolescents than in controls. However, we found no association between vitamin D levels and carotid intima media thickness.

Matter et al[22] studied healthy adolescents to evaluate the effect of vitamin D deficiency on myocardial function and other echocardiographic variables. They reported that no significant differences were found in the right ventricular diameter at end diastole, left ventricular diameter at end systole, interventricular septal thickness at diastole, interventricular septal thickness at systole, left ventricular posterior wall thickness at diastole, or left ventricular posterior wall thickness at systole between vitamin D-deficient adolescents and controls. However, in the vitamin D-deficient group, they found significantly increased left ventricular diameter at the end of diastole. They also found that left ventricular systolic function, measured by fractional shortening, showed no significant difference between the groups.

Fall et al[42] found that higher circulating vitamin D concentrations were associated with better systolic left ventricular function and smaller left ventricular end systolic diameter in subjects without prior heart failure at age 70 at baseline. Over 5 years of follow-up, measures of cardiac geometry tended to increase, and measures of left ventricular systolic and diastolic functions tended to decrease. However, they did not observe any significant association between vitamin D levels at age 70 and echocardiographic measures at age 75. Pekkanen et al[43] reported that low vitamin D levels were independently associated with reduced left ventricular ejection fraction and increased left atrial diameter. In contrast, some authors have reported that serum vitamin D levels were not significantly associated with left ventricular structure and function.[28,44,45]

In our study, comparing all the echocardiographic parameters, mean values did not differ significantly between the groups, except

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for interventricular septal thickness at the diastole and left ventricular posterior wall thickness at the diastole, which had higher values in the controls. Additionally, we found no association between vitamin D level and cardiac structure and function, except a negative association was found in the left atrial diameter, which was similarly reported by Pekkanen et al.[43]

In addition to the conventional Doppler method, Tissue Doppler Imaging (TDI) is a useful diagnostic tool for myocardial function. Matter et al[22] showed decreased atrioventricular Sm velocities together with higher isovolumic contraction time for both left and right ventricles in vitamin D-deficient adolescents, indicating left and right ventricle systolic dysfunction in this age group. Moreover, they found that TDI indexes of global myocardial function (left and right ventricle Tei indexes) were significantly higher in the vitamin D-deficient group. Finally, they reported that serum vitamin D levels were negatively correlated with right and left ventricle Tei indexes, while there was a positive correlation with mitral peak Sm velocity.

Armstrong et al[46] concluded that in neonates with severe vitamin D deficiency, there was no impairment in myocardial contractility when comparing these neonates to those with normal levels using TDI measures.

In our study, it was seen that left ventricle myocardial normal $_{\text{septal, lateral}}$ values and systolic function measured by ejection fraction and tissue Doppler imaging were preserved in the vitamin D-deficient adolescents and control group. Additionally, tricuspid lateral wall myocardial $_{\text{tricuspid}}$ and tricuspid annular plane systolic excursion, which indicate right ventricular systolic function, were found to be within normal ranges in vitamin D-deficient and control patients, in keeping with many studies.

It has been suggested in experimental studies that vitamin D can regulate the growth and proliferation of cardiomyocytes and vascular smooth muscle cells.[42] Low vitamin D levels were associated with cardiac hypertrophy, which leads to diastolic dysfunction. Pekkanen et al[43] found that low vitamin D levels were associated with impaired left ventricular filling (high E/E') and low E/A mitral flow patterns in nondiabetic patients with stable coronary artery disease. Matter et al[22] found alterations in Em and Am velocities and Em/Am, E/Em and tricuspid E/Em in the right and left ventricles in vitamin D-deficient adolescents, which indicated diastolic dysfunction. Additionally, they reported significantly higher right and left ventricle Tei indexes in the vitamin D-deficient group, indicating compromised global systolic and diastolic functions. They also showed that, as written above, serum vitamin D levels were negatively correlated with right and left ventricle Tei indexes. In contrast, van Ballegooijen et al[45] showed no strong association of vitamin D with myocardial structure and function.

In our study, we found similar values in E/A mitral and E/A tricuspid ratios in vitamin D-deficient adolescents compared with the controls. We also found no significant alterations in right and left ventricle Tei indexes in either group. Additionally, we showed no association of vitamin D level with E/A mitral and E/A tricuspid raitos and right and left ventricle Tei indexes in both groups.

Conclusion

The results of this study demonstrate that vitamin D deficiency in female adolescence is associated with normal myocardial geometry and function. Conducting a study with a longitudinal design in the future should explain the prognostic significance of the structural and functional changes in the left and right ventricles in patients with vitamin D deficiency. Although it has been associated with normal levels of asymmetric dimethyl arginine concentration, high measured carotid intima-media thickness may reflect endothelial dysfunction.

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Competing interest. None.

References

1. Maalouf NM. The noncalciotropic actions of vitamin D: recent clinical developments. Curr Opin Nephrol Hypertens 2008; 17: 408–415.
2. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao LP. 1,25-dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002; 110: 229–238.
3. Chen S, Law CS, Grigsby CL, et al. Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. Circulation 2011; 201: 1838–1847.
4. De Gennaro Colonna V, Bianchi M, Pascale V, et al. Asymmetric dimethylarginine (ADMA): an endogenous inhibitor of nitric oxide synthase and a novel cardiovascular risk molecule. Med Sci Monit 2009; 15: 91–101.
5. Bouras G, Deftereos S, Tousoulis D, et al. Asymmetric dimethylarginine (ADMA): a promising biomarker for cardiovascular disease? Curr Top Med Chem 2013; 13: 180–200.
6. London GM, Guérin AP, Verbeke FH, et al. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. J Am Soc Nephrol 2007; 18: 613–620.
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and betacell function from fasting plasma glucose and insulin concentrations in men. Diabetologia 1985; 28: 412–429.
8. Chen XM, Hu CP, Li YJ, Jiang JL. Cardiovascular risk in autoimmune disorders: role of asymmetric dimethylarginine. Eur J Pharmacol 2012; 696: 5–11.
9. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and therapeutics committee of the lawson wilkins pediatric endocrine society. vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122: 398–417.
10. Sahn DJ, De Maria A, Kisslo J, Weyman A. The committee on M-mode standardization of the American society of echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072–1083.
11. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992; 20: 1251–1260.
12. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function— a study in normals and dilated cardiomyopathy. J Cardiol 1995; 26: 357–366.
13. Jurcut R, Giusca S, La Gerche A, Vasile S, Ginghina C, Voigt JU. The echocardiographic assessment of the right ventricle: what to do in 2010? Eur J Echocardiogr 2010; 11: 81–96.
14. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. Kidney Int 2008; 74: 170–179.
15. Tomaschitz A, Pilz S, Ritz E, et al. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: the ludwigshafen risk and cardiovascular health (LURIC) study. Clin Chim Acta 2010; 411: 1354–1360.
16. Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010; 55: 1283–1288.
17. Resnick LM, Müller FB, Laragh JH. Calcium-regulating hormones in essential hypertension. Relation to plasma renin activity and sodium metabolism. Ann Intern Med 1986; 105: 649–654.

https://doi.org/10.1017/S1047951123001257 Published online by Cambridge University Press

18. Pacifico L, Anania C, Osborn JF, et al. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in caucasian children and adolescents. Eur J Endocrinol 2011; 165: 603–611.
19. Khayyatzadeh SS, Mirmoosavi SJ, Fazeli M, et al. High-dose vitamin D supplementation is associated with an improvement in several cardiometabolic risk factors in adolescent girls: a nine-week follow-up study. Ann Clin Biochem 2018; 55: 227–235.
20. Hauger H, Laursen RP, Ritz C, Mølgaard C, Lind MV, Damsgaard CT. Effects of vitamin D supplementation on cardiometabolic outcomes in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. Eur J Nutr 2020; 59: 873–884.
21. Wamberg L, Kampmann U, Stødkilde-Jørgensen H, Rejnmark L, Pedersen SB, Richelsen B. Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - results from a randomized trial. Eur J Intern Med 2013; 24: 644–649.
22. Matter M, El-Sherbiny E, Elmougy A, Abass M, Aldossary S, Ali WA. Myocardial function in Saudi adolescents with vitamin D deficiency: tissue doppler imaging study. J Saudi Heart Assoc 2016; 28: 22–30.
23. Rusconi RE, De Cosmi V, Gianluca G, Giavoli C, Agostoni C. Vitamin D insufficiency in obese children and relation with lipid profile. Int J Food Sci Nutr 2015; 66: 132–134.
24. Lee SH, Kim SM, Park HS, et al. Serum 25-hydroxyvitamin D levels, obesity and the metabolic syndrome among Korean children. Nutr Metab Cardiovasc Dis 2013; 23: 785–791.
25. Hirschler V, Molinari C, Maccallini G, Intersimone P, Gonzalez CD. Vitamin D levels and cardiometabolic markers in indigenous argentinean children living at different altitudes. Glob Pediatr Health 2019; 8; 6: 2333794X18821942.
26. Jiang X, Peng M, Chen S, Wu S, Zhang W. Vitamin D deficiency is associated with dyslipidemia: a cross-sectional study in 3788 subjects. Curr Med Res Opin 2019; 35: 1059–1063.
27. Sharba ZF, Shareef RH, Abd BA, Hameed EN. Association between dyslipidemia and vitamin D deficiency: a cross-sectional study. Folia Med (Plovdiv) 2021; 63: 965–969.
28. Colak R, Anil M, Yasar F, et al. Metabolic disturbances and cardiovascular risk factors in obese children with vitamin D deficiency. Arch Pediatr 2020; 27: 140–145.
29. Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. Prog Lipid Res 2011; 50: 303–312.
30. Berridge MJ. Vitamin D deficiency and diabetes. Biochem J 2017; 474: 1321–1332.
31. Xiao P, Dong H, Li H, et al. Adequate 25-hydroxyvitamin D levels are inversely associated with various cardiometabolic risk factors in Chinese children, especially obese children. BMJ Open Diabetes Res Care 2020; 8: e000846.
32. Niroomand M, Fotouhi A, Irannejad N, Hosseinpanah F. Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. Diabetes Res Clin Pract 2019; 148: 1–9.
33. Sethuraman U, Zidan MA, Hanks L, Bagheri M, Ashraf A. Impact of vitamin D treatment on 25 hydroxy vitamin D levels and insulin homeostasis in obese African American adolescents in a randomized trial. J Clin Transl Endocrinol 2018; 12: 13–19.
34. Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. J Clin Endocrinol Metab 2009; 94: 4023–4030.
35. Salum E, Kampus P, Zilmer M, et al. Effect of vitamin D on aortic remodeling in streptozotocin-induced diabetes. Cardiovasc Diabetol 2012; 11: 58.
36. Bednarek-Skublewska A, Smoleń A, Jaroszyński A, Załuska W, Ksiazek A. Effects of vitamin D3 on selected biochemical parameters of nutritional status, inflammation, and cardiovascular disease in patients undergoing long-term hemodialysis. Pol Arch Med Wewn 2010; 120: 167–174.
37. Choi HR, Lee SW, Yeom H, Jeon DH, Kim HC, Youm Y. Association between vitamin D status and asymmetric dimethylarginine (ADMA) concentration in the Korean elderly population. Maturitas 2017; 102: 13–17.
38. Taskiran B, Cansu GB, Bahadir E, Mutluay R. Role of vitamin D in intima media thickness in patients with Type 1 Diabetes mellitus. J Natl Med Assoc 2017; 109: 14–20.
39. Monteiro Júnior FC, Mandarino NR, Santos EM, et al. Correlation between serum 25-hydroxyvitamin D levels and carotid intima-media thickness in a Brazilian population descended from African slaves. Braz J Med Biol Res 2018; 51: e7185.
40. Aydin E, Altin C, Özcan Söylev G, Tekindal MA, Ağildere M. Assessment of subclinical atherosclerosis in vitamin D deficiency. Ultrasound Q 2019; 35: 142–146.
41. Chen FH, Liu T, Xu L, Zhang L, Zhou XB. Association of serum vitamin D level and carotid atherosclerosis: a systematic review and meta-analysis. J Ultrasound Med 2018; 37: 1293–1303.
42. Fall T, Shiue I, Bergeå af Geijerstam P, et al. Relations of circulating vitamin D concentrations with left ventricular geometry and function. Eur J Heart Fail 2012; 14: 985–991.
43. Pekkanen MP, Ukkola O, Hedberg P, et al. Serum 25-hydroxyvitamin D is associated with major cardiovascular risk factors and cardiac structure and function in patients with coronary artery disease. Nutr Metab Cardiovasc Dis 2015; 25: 471–478.
44. Nolte K, Herrmann-Lingen C, Platschek L, et al. Vitamin D deficiency in patients with diastolic dysfunction or heart failure with preserved ejection fraction. ESC Heart Fail 2019; 6: 262–270.
45. van Ballegooijen AJ, Snijder MB, Visser M, et al. Vitamin D in relation to myocardial structure and function after eight years of follow-up: the Hoorn study. Ann Nutr Metab 2012; 60: 69–77.
46. Armstrong K, Onwunmeme C, Franklin O, Molloy E. Vitamin D levels and myocardial function in preterm infants. Arch Dis Child 2012; 97: A323–A323.

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