

Myocardial function in Saudi adolescents with vitamin D deficiency: Tissue Doppler imaging study



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Vitamin D deficiency is a common health problem in Saudi Arabia especially in children and adolescents. Many studies have reported the relation between low 25-Hydroxyvitamin D (25(OH)D) levels with cardiovascular diseases risk factors as well as cardiovascular events, including stroke, myocardial infarction, and congestive heart failure. This study was conducted to evaluate the effect of 25(OH)D deficiency on the myocardial function and other echocardiographic variables in adolescent, using tissue Doppler imaging (TDI) and to correlate these parameters with 25(OH)D level. The study included 84 healthy adolescents, consecutively selected from adolescents attending the outpatient clinic of Saad Specialist Hospital, KSA between September 2013 and October 2014. The study population was classified into two groups; vitamin D deficient group with 25(OH)D level less than 20 ng/mL and normal vitamin D (control group) with 25(OH)D equal or more than 30 ng/mL. Both groups were subjected to measuring hemoglobin level, serum albumin, creatinine, total calcium, Phosphorous, intact parathyroid hormone (iPTH), B-type natriuretic peptide (BNP), and 25(OH)D levels. Both conventional and pulsed wave TDI were done for all participants. TDI measurements showed significant higher LV Tei Index and RV Tei index when compared to the control group (0.61 ± 0.11 Vs 0.32 ± 0.05 $p < 0.0001$), (0.54 ± 0.14 Vs 0.40 ± 0.06 $p < 0.0001$) respectively. Mitral and tricuspid annular systolic velocities were significantly lower in vitamin D deficient group (6.99 ± 1.92 Vs 10.69 ± 0.31 cm/sec $p < 0.0001$ and 12.30 ± 2.14 Vs 13.89 ± 0.29 $p < 0.0001$ respectively). The mitral and tricuspid E/Em ratio was significantly higher in vitamin D deficient group than control group ($p < 0.0001$, $p 0.005$) respectively. Left ventricular internal diameter at end-diastole (LVIDd) was significantly higher in vitamin D deficient group (44.72 ± 6.33 Vs 40.36 ± 6.21 $p 0.003$). Serum 25 (OH)D level showed significant negative correlation with LV Tei index ($r = -0.668$, $p < 0.0001$), RV Tei index ($r = -0.421$, $p < 0.0001$). Vitamin D deficiency is associated with subtle systolic and diastolic myocardial dysfunction in Saudi adolescents. TDI is a useful tool for detecting early changes in the myocardium in this particular group.

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Introduction

Calcifediol, also known as 25-hydroxyvitamin D (25(OH)D) plays an important role in the maintenance of bone health, principally via its effects on calcium metabolism. In the past decade, a growing body of evidence has suggested that 25(OH)D may also play an important homeostatic role in other organ systems [1]. This hypothesis is supported by the broad tissue distribution of 25(OH)D receptors in nonskeletal organs [2,3]. Accordingly, inadequate 25(OH)D status may have extraskelatal as well as skeletal consequences. More recent evidence suggests that 25(OH)D may also play a protective role in many chronic conditions, including cancer, autoimmune, kidney, and cardiovascular diseases (CVD) [4].

Vitamin D deficiency is defined as a 25(OH)D level of <20 ng/mL and insufficiency as <30 ng/mL but >20 ng/mL. A level \geq 30 ng/mL is considered sufficient [5]. Observational studies have associated low 25(OH)D levels with CVD risk factors, including hypertension, hyperlipidemia, diabetes, and metabolic syndrome, as well as with cardiovascular events, including stroke, myocardial infarction, and congestive heart failure [6].

There are several mechanisms by which 25(OH)D may be associated with atherosclerosis and CVD events and numerous recent studies have found high rates of CVD among patients with lower levels of 25(OH)D [7,8].

The aim of this study was to evaluate the effect of a 25(OH)D deficiency on the myocardial function and other echocardiographic variables in healthy adolescents, using tissue Doppler imaging (TDI) and to correlate these parameters with 25(OH)D level.

Material and methods

This was a prospective study, performed between September 2013 and October 2014. Written informed consent was obtained from the family or the legal representative of the adolescent participating in this study. The Institutional Review Board of Saad Specialist Hospital approved the study.

Our study population consisted of 84 healthy adolescents, consecutively selected from adolescents attending the outpatient clinic of Saad Specialist Hospital, KSA.

All the participants were healthy, and attended only for a school medical check-up before the first

Abbreviations

25 (OH) D	25-Hydroxyvitamin D
BNP	B-type natriuretic peptide
BSA	Body Surface Area
BW	Body weight
CVD	cardiovascular diseases
DBP	diastolic blood pressure
DT	deceleration time
FS	fractional shortening
ICT	isovolumetric contraction time
iPTH	intact parathyroid hormone
IRT	isovolumetric relaxation time
IVSd	interventricular septal thickness at diastole
IVSs	interventricular septal thickness at systole
LVIDd	left ventricular diameter at end diastole
LVIDs	left ventricular diameter at end systole
LVPWd	left ventricular posterior wall thickness at diastole
LVPWs	left ventricular posterior wall thickness at systole
RVDd	right ventricular diameter at end diastole
SBP	systolic blood pressure
TDI	tissue Doppler imaging

semester; their ages ranged from 12 years to 16 years. We excluded anyone with acute or chronic disease, under treatment that could influence their 25(OH)D level, or adolescents with 25(OH)D levels of 20–30 ng/mL. According to the level of a 25(OH)D, the study population was classified into two groups: the vitamin D deficient group, with 25(OH)D level <20 ng/mL; and the control group with normal vitamin D, with 25(OH)D \geq 30 ng/mL.

All the studied adolescents were subjected to complete history taking, thorough clinical examination, and laboratory tests including: hemoglobin level, serum albumin, creatinine, total calcium, phosphorous, intact parathyroid hormone (iPTH), B-type natriuretic peptide (BNP), and 25(OH)D levels. The serum concentration of 25(OH)D was measured using radioimmunoassay (reference range, 9.0–37.6 ng/mL) [9].

Echocardiographic measurements

Echocardiographic measurements were done using (SONOS-5500; Hewlett Packard, Andover, MA, USA) with an 8 MHz probe incorporating color flow, pulsed wave, continuous wave Doppler, and pulsed-wave TDI. Images were recorded on videotape. All measurements were performed by a single investigator (M.M.), who was blinded to the patients' 25(OH)D status. The details of conventional echocardiography and TDI measurements were as previously described [10]. All parameters were measured during end

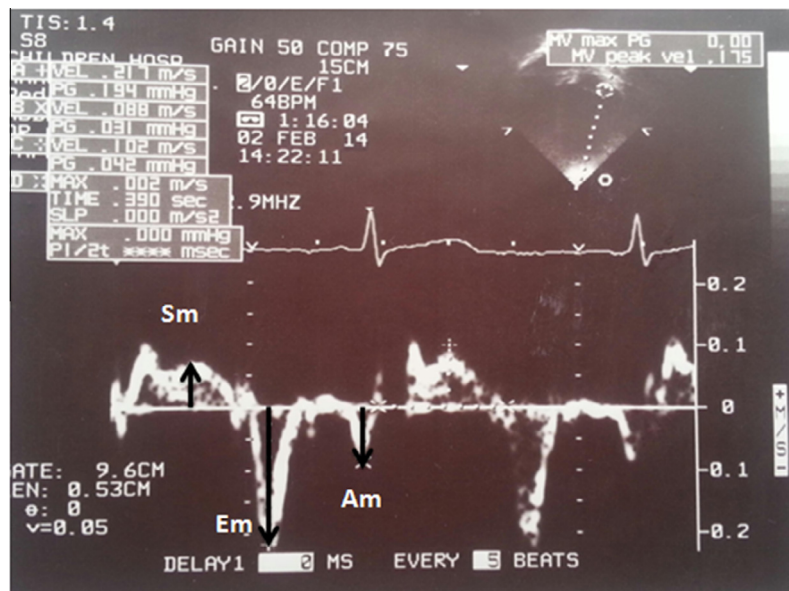


Figure 1. Example of calculations of mitral annular tissue Doppler imaging velocity measurements. Am = late diastolic annular velocity; Em = early diastolic annular velocity; Sm = peak systolic annular velocity.

expiration and three consecutive cardiac cycles were measured and averaged for each measurement [11]. TDI recordings were adequately obtained in all patients (Fig. 1). TDI parameters indicative of the systolic function included peak annular systolic (Sm) velocity and isovolumetric contraction time (ICT). Variables indicative of diastolic function included early annular diastolic velocity (Em), late annular diastolic velocity (Am), Em/Am ratio, the ratio of early filling velocity (E)/Em ratio, and isovolumetric relaxation time (IRT). Variables indicative of global myocardial dysfunction included the Tei index. The intraobserver variability for measurements of mitral Sm velocity, tricuspid Sm velocity, right ventricular (RV) Tei index, and left ventricular

(LV) Tei index showed high correlation coefficients and low variability ($r = 0.84$ for mitral Sm velocity, $r = 0.91$ for tricuspid Sm velocity, $r = 0.94$ for LV Tei index, and $r = 0.93$ for RV Tei index).

Statistical analysis

Data are presented as mean \pm standard deviation. The Chi-square test (or Fisher exact test for expected value of <5) was used for analysis of categorical variables. Continuous variables with Gaussian distribution were analyzed using the unpaired t test for between-group comparisons. For continuous variables with non-Gaussian distribution, the Mann-Whitney U test was used for between-group analyses. Pearson's correlation

Table 1. Clinical and laboratory characteristics of the studied groups.

	Vitamin D deficient group (n = 30)	Control group (n = 54)	p
Age (y)	14.08 \pm 2.01	13.93 \pm 1.06	0.82
Male ratio	24 (60%)	29 (72%)	–
BW (kg)	32.49 \pm 8.72	31.63 \pm 9.04	0.66
Height (cm)	135.43 \pm 17.29	131.35 \pm 12.72	0.23
BSA (m ²)	1.10 \pm 0.20	1.06 \pm 0.18	0.38
SBP (mmHg)	110.50 \pm 15.07	113.50 \pm 12.25	0.76
DBP (mmHg)	81.00 \pm 11.78	79.88 \pm 11.59	0.06
Hemoglobin (g/dL)	13.0 \pm 1.2	12.0 \pm 1.1	0.87
Serum albumin (g/dL)	4.42 \pm 1.12	4.62 \pm 0.85	0.51
Serum creatinine (mg/dL)	0.9 \pm 0.2	0.8 \pm 0.3	0.18
25(OH)D level (ng/mL)	17.62 \pm 4.6	36.20 \pm 1.4	<0.000
Serum phosphorus (mg/dL)	4.14 \pm 0.37	3.89 \pm 0.95	0.38
Serum calcium (mg/dL)	7.83 \pm 1.36	9.77 \pm 0.96	<0.000
iPTH (pg/mL)	70.5 \pm 5.25	42.12 \pm 3.23	<0.000
BNP level (pg/mL)	33.62 \pm 11.14	10.07 \pm 1.92	<0.000

25(OH)D = 25 hydroxyvitamin D; BNP = B type natriuretic peptide; BSA = body surface area; BW = body weight; DBP = diastolic blood pressure; iPTH = intact parathyroid hormone; SBP = systolic blood pressure.

coefficient was used to test the relationship between serum 25(OH)D level and other parameters.

Results

We studied 84 healthy adolescents aged 12–16 years; the vitamin D deficient group included 30 adolescents (age 14.08 ± 2.01 years), while the remaining 54 adolescents (age 13.93 ± 1.06 years) were in the control group. Demographic, clinical, and laboratory data for the groups studied are shown in Table 1. There were no significant differences between groups regarding age, body weight, height, body surface area, systolic blood pressure, and diastolic blood pressure. Additionally, no significant differences were reported in hemoglobin, serum creatinine, albumin, and phosphorous levels between both groups. The vitamin D deficient group showed significant lower serum 25(OH)D and total serum calcium levels when compared with the second group ($p < 0.0001$). There were significantly higher serum iPTH and BNP levels in the vitamin D deficient group when compared with the second group ($p < 0.0001$).

Two-dimensional, M-mode, and conventional Doppler echocardiographic parameters of the studied groups are given in Table 2. No significant differences were found in 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 both groups, but there was significantly increased left ventricular diameter at end diastole in the vitamin D deficient group ($p = 0.003$). Left ventricular systolic function, measured by fractional shortening (FS), showed no significant difference between groups.

Left ventricular diastolic function evaluated by conventional Doppler method showed no significant differences in mitral early (E), late (A) diastolic velocities, mitral E/A ratio, mitral isovolumetric relaxation time, and mitral deceleration time between groups. Diastolic evaluation of the right ventricle showed no significant difference in tricuspid E and A diastolic velocities, tricuspid E/A ratio, or tricuspid deceleration time.

TDI

TDI parameters of both lateral mitral annulus and lateral tricuspid annulus are shown in Table 3. We found significantly lower Sm velocity ($p < 0.0001$), Em velocity ($p < 0.0001$), and mitral annular Em/Am ratio ($p < 0.0001$) but higher Am velocity ($p = 0.009$) in the vitamin D deficient group in comparison to the control group. The vitamin D deficient group had significantly prolonged mitral IRT ($p < 0.0001$) and mitral ICT ($p < 0.0001$) compared with controls. The mitral E/Em ratio was significantly higher in vitamin D

Table 2. Two-dimensional, M mode and conventional Doppler echocardiographic parameters between the studied groups.

	Vitamin D deficient group (n = 30)	Control group (n = 54)	p
RVDd (mm)	10.83 ± 2.69	11.81 ± 2.63	0.10
LVIDd (mm)	44.72 ± 6.33	40.36 ± 6.21	0.003
LVIDs (mm)	29.25 ± 6.84	26.75 ± 4.82	0.06
IVSd (mm)	10.50 ± 3.38	11.21 ± 2.92	0.07
IVSs (mm)	12.77 ± 3.32	11.73 ± 2.75	0.13
LVPWd (mm)	8.67 ± 2.95	9.92 ± 3.02	0.09
LVPWs (mm)	9.87 ± 2.93	10.15 ± 3.05	0.08
FS (%)	33.17 ± 5.55	34.84 ± 8.55	0.32
Mitral inflow			
E wave (m/s)	1.16 ± 0.23	0.91 ± 0.14	0.06
A wave (m/s)	1.02 ± 0.20	0.86 ± 0.12	0.07
E/A ratio	1.07 ± 0.39	0.97 ± 0.25	0.81
IVRT (ms)	79.38 ± 13.45	75.60 ± 4.79	0.27
DT (ms)	199.25 ± 37.03	184.25 ± 11.49	0.74
Tricuspid inflow			
E wave (m/s)	0.64 ± 0.16	0.65 ± 0.13	0.84
A wave (m/s)	0.56 ± 0.19	0.50 ± 0.12	0.08
E/A ratio	1.24 ± 0.38	1.33 ± 0.28	0.23
DT (ms)	113.38 ± 35.05	111.28 ± 34.52	0.99

DT = deceleration time; FS = fraction shortening; IVRT = isovolumetric relaxation time; IVSd = interventricular septal thickness at diastole; IVSs = interventricular septal thickness at systole; LVIDd = left ventricular diameter at end diastole; LVIDs = left ventricular diameter at end systole; LVPWd = left ventricular posterior wall thickness at diastole; LVPWs = left ventricular posterior wall thickness at systole; RVDd = right ventricular diameter at end diastole.

Table 3. Tissue Doppler imaging-derived variables between the studied groups.

	Vitamin D deficient group (n = 30)	Control group (n = 54)	p
Mitral annulus			
Sm (cm/s)	6.99 ± 1.92	10.69 ± 0.31	<0.0001
Em (cm/s)	10.27 ± 1.84	18.63 ± 1.38	<0.0001
Am (cm/s)	13.39 ± 2.49	11.67 ± 3.19	0.009
Em/Am ratio	0.77 ± 0.12	1.72 ± 0.514	<0.0001
ICT (ms)	85.12 ± 12.49	77.36 ± 1.39	<0.0001
IRT (ms)	88.00 ± 16.20	62.38 ± 2.39	<0.0001
Mitral E/Em	8.51 ± 2.17	5.90 ± 0.98	<0.0001
Tricuspid annulus			
Sm (cm/s)	12.30 ± 2.14	13.89 ± 0.29	<0.0001
Em (cm/s)	13.21 ± 3.45	16.29 ± 1.29	<0.0001
Am (cm/s)	15.97 ± 5.49	10.54 ± 1.43	<0.0001
Em/Am ratio	0.89 ± 0.31	1.54 ± 0.07	<0.0001
ICT (ms)	62.62 ± 11.98	57.60 ± 8.85	0.040
IRT (ms)	68.25 ± 13.05	61.58 ± 2.11	0.002
Tricuspid E/Em	5.71 ± 1.01	4.03 ± 0.6	0.005
LV Tei index	0.61 ± 0.11	0.32 ± 0.05	<0.0001
RV Tei index	0.54 ± 0.14	0.40 ± 0.06	<0.0001

Am = late diastolic annular velocity; E/Em = ratio of early filling velocity wave/early diastolic annular velocity; Em = early diastolic annular velocity; ICT = isovolumetric contraction time; IRT = isovolumetric relaxation time; LV = left ventricular; RV = right ventricular; Sm = peak systolic annular velocity.

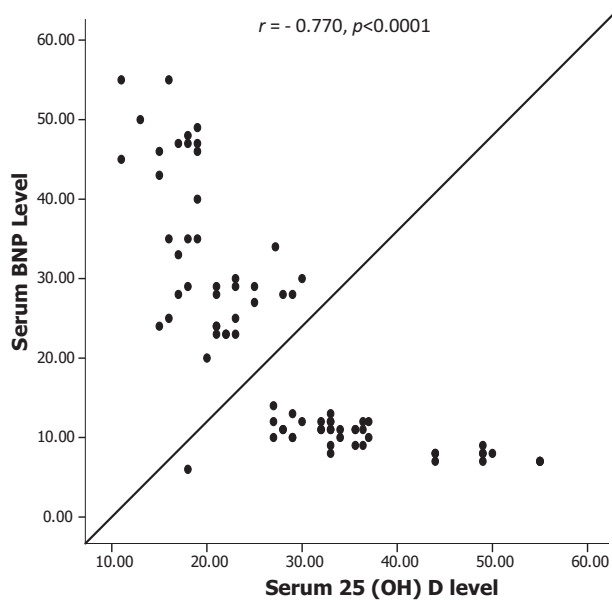


Figure 2. Negative correlation between serum 25-hydroxyvitamin D (25(OH)D) level and serum B type natriuretic peptide (BNP) level.

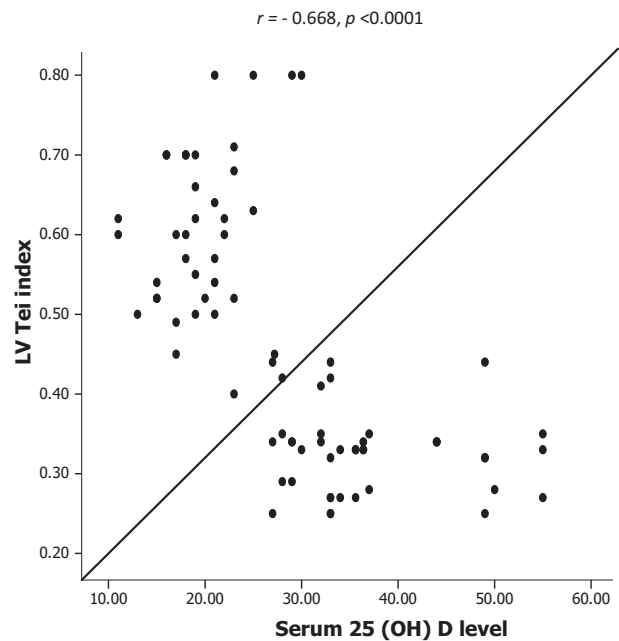


Figure 3. Negative correlation between serum 25-hydroxyvitamin D (25(OH)D) level and tissue Doppler imaging-derived left ventricular (LV) Tei index.

deficient group than control group ($p < 0.0001$). Similar findings were observed at the lateral tricuspid annulus: significant lower tricuspid annular Sm velocity ($p < 0.0001$), tricuspid annular early diastolic velocity (Em) ($p < 0.0001$), and tricuspid annular Em/Am ratio ($p < 0.0001$), but higher tricuspid Am velocity ($p < 0.0001$) and higher tricuspid E/Em ratio ($p = 0.005$) in the vitamin D deficient group compared with the control group. Both Tricuspid ICT and ICT were significantly prolonged in the vitamin D deficient

adolescents when compared with control group ($p = 0.04$) and ($p = 0.002$) respectively. Myocardial performance index (Tei index) of the LV and RV derived by TDI was significantly higher in the studied group than the control group (both $p < 0.0001$).

Serum 25(OH)D level showed significant negative correlation with serum BNP level ($r = -0.770$, $p < 0.0001$; Fig. 2), LV Tei index ($r = -0.668$,

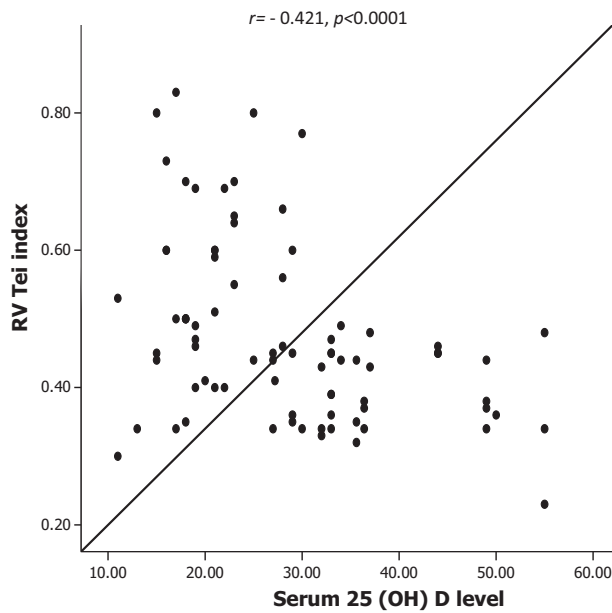


Figure 4. Negative correlation between serum 25-hydroxyvitamin D (25(OH)D) level and tissue Doppler imaging-derived right ventricular (RV) Tei index.

$p < 0.0001$; Fig. 3), RV Tei index ($r = -0.421$, $p < 0.0001$; Fig. 4) and LVIDd ($r = -0.320$, $p = 0.004$; Fig. 5), while significant positive correlation was found between serum 25(OH)D level and mitral annular Sm velocity ($r = 0.606$, $p < 0.0001$; Fig. 6). By contrast, no significant correlation was found between serum 25(OH)D level and FS ($r = -0.091$, $p = 0.42$).

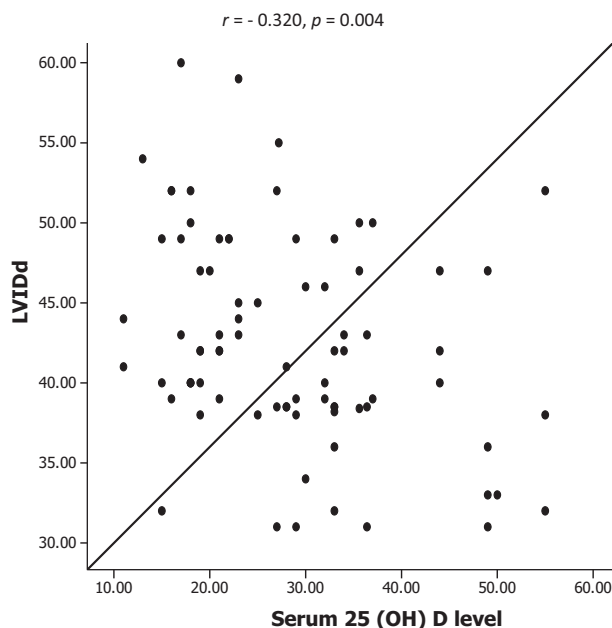


Figure 5. Negative correlation between serum 25-hydroxyvitamin D (25(OH)D) level and left ventricular diameter at end diastole (LVIDd).

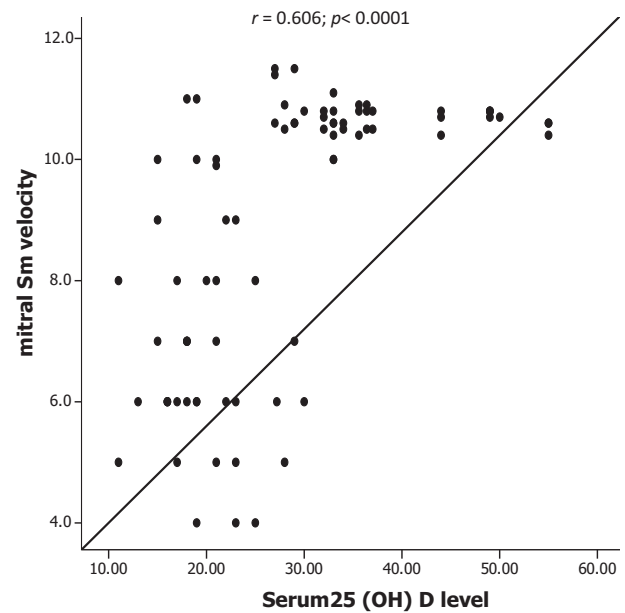


Figure 6. Positive correlation between serum 25-hydroxyvitamin D (25(OH)D) level and tissue Doppler imaging-derived mitral peak systolic annular (Sm) velocity.

Discussion

To the best of our knowledge, this is the first study to assess the utility of TDI in healthy adolescents with vitamin D deficiency. Our results support the use of TDI as a useful diagnostic tool for myocardial dysfunction in those patients. Decreased atrioventricular Sm velocities together with higher ICT for both left and right ventricles in vitamin D deficient adolescents indicated LV and RV systolic dysfunction in this age group. The changes in atrioventricular Em and Am velocities, Em/Am ratio, E/Em ratio and IRT indicated altered diastolic function in the vitamin D deficient group. The E/Ea ratio is the best parameter to predict the mean LV filling pressures [12], and it is proportional to the severity of LV diastolic dysfunction. It showed significant alteration in the vitamin D deficient group compared with the control and together with significant reduced mitral Em velocity gave important information about the diastolic function of the LV. Similar tricuspid E/Em ratio alteration has been noted, indicating changes in the right ventricular diastolic function in the vitamin D deficient group. The TDI indexes of global myocardial function (RV and LV Tei indexes) were significantly higher in the vitamin D deficient group, indicating compromised global systolic and diastolic function. TDI was more sensitive than conventional echocardiography in detecting global myocardial dysfunction. Tei index has been reported to be useful for the assessment of global function of each

ventricle, independent of heart rate, blood pressure, or ventricular geometry [13,14]. It has been used to analyze systolic and diastolic global ventricular function in various congenital and acquired cardiac abnormalities in neonates and children [14]. We have demonstrated that serum 25(OH)D levels correlated negatively with RV and LV Tei indexes, while there was a positive correlation with mitral peak Sm velocity. By contrast, no significant correlation was found between serum 25(OH)D level and FS. Conventional echocardiography appeared to be less valuable for the early detection of abnormal myocardial function in patients with vitamin D deficiency as there were no statistically significant differences in systolic and diastolic function of LV and RV. Armstrong et al. studied myocardial contractility in neonates with severe vitamin D deficiency using TDI measures of systolic and diastolic velocity and concluded that severe vitamin D deficiency appears to cause no impairment in myocardial contractility when comparing these neonates to those with normal levels [15]. A study of left ventricular function in infants and children with nutritional vitamin D deficiency rickets demonstrated echocardiographic evidence of left ventricular dysfunction. These abnormalities were not, however, sufficiently severe to be associated with clinical signs of cardiac failure. This finding may return to normal following adequate treatment of the rickets [16]. Two-dimensional echocardiography was used to measure the left ventricular mass index, E/A ratio, Em, E/Em ratio, and myocardial performance index in pediatric patients with chronic kidney disease and nutritional vitamin D deficiency. These patients showed increased left ventricular mass and severe diastolic dysfunction, which may be irreversible [17]. It has been postulated that vitamin D affects cardiovascular function via multiple mechanisms. Experimental studies have suggested that vitamin D can regulate the growth and proliferation of cardiomyocytes and vascular smooth muscle cells. It has been shown in neonatal rat hearts that activated vitamin D might act via a protein kinase-dependent mechanism to inhibit cardiomyocytes maturation [18] and proliferation [19]. Observational studies support the concept that vitamin D deficiency is involved in the pathogenesis of congestive heart failure [20].

We found significant negative correlation between serum 25(OH)D and serum BNP levels. In studies of experimental animals, activation of nuclear vitamin D receptors by 1,25(OH)2D3 suppresses the expression and secretion of atrial

natriuretic peptide (ANP) and BNP in cardiac myocytes [21,22], while in clinical studies of non-dialysis chronic kidney disease patients, individuals treated with 1,25(OH)2D3 for 12 weeks were observed to have improved left ventricular diastolic function as compared with placebo [23]. In animal models of heart failure, active vitamin D treatment was shown to reduce cardiac hypertrophy, attenuate myocardial dysfunction and suppressed the secretion of the cardiac natriuretic peptides [24]. Several genes that are upregulated in the course of cardiac hypertrophy, involving those of natriuretic peptides and renin, are down-regulated by vitamin D [24]. Importantly, there exists increasing molecular and clinical evidence that a sufficient vitamin D status is required for maintenance of diastolic function of the heart [24,25]. Although vitamin D supplementation in adults with congestive heart failure did not improve physical performance as measured by peak oxygen consumption [26], there are several case reports of vitamin D deficient children with dilated cardiomyopathy that could be successfully treated with vitamin D and calcium [27]. Vitamin D supplementation was beneficial in treatment of congestive heart failure, as demonstrated by a recent double-blind placebo-controlled study [28].

Lower serum calcium level together with higher iPTH level was found in vitamin D deficient adolescents. The inverse relationship of increasing iPTH with decreasing 25(OH)D concentrations has been demonstrated in older children and adolescents [29]. The extent of vitamin D deficiency has been suggested by reports from other regions of the world, including children and adolescents living in Germany, Turkey, Finland, and Ireland [30–32]. With lower 25(OH)D concentrations correlating with increased iPTH concentrations, vitamin D deficiency could result in secondary hyperparathyroidism. This condition would deplete the bone of mineral, especially during periods of accelerated bone growth, and lead to long-term detrimental effects [33].

Solar UV-B radiation is the major source of vitamin D for humans. Consequently, the vitamin D status is largely influenced by season, geographic latitude, daily outdoor activities, and the percentage of body surface exposed to solar UV-B. A significant proportion of individuals in Europe and North America have vitamin D concentrations in the deficiency range [25(OH)D < 25 nM]. Available data indicate that low solar UV-B exposure and/or low 25(OH)D concentrations are associated with an increased risk of cardiovascular diseases [34]. Vitamin D deficiency is common in

healthy Saudi adults and more pronounced in women and in younger age groups [34]. The lack of sun exposure in eastern area in Saudi Arabia due to the wearing of traditional clothes and deliberate avoidance of the sun, and inadequate dietary intake are likely to be the principal causes of low vitamin D levels. Adolescents are at high risk of vitamin D deficiency due to the increased metabolic demand of rapid growth during this period, so pediatricians and other health care professionals should strive to make vitamin D supplements readily available to all children and adolescents and encourage sun exposure where possible.

Limitations

This study included a small number of patients, so we believe that multicenter studies with an adequate number of patients is required to power the study sufficiently and further delineate the relationship between serum vitamin D level and myocardial function. Additionally, TDI is angle dependent, so recent modalities of echocardiographic assessment of left and right ventricles can be used including strain rate imaging.

Conclusion

Vitamin D deficiency is associated with subtle systolic and diastolic myocardial dysfunction in Saudi adolescents. TDI is a useful tool for detecting early changes in the myocardium in this particular group.

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