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The relationship between vitamin D level and echocardiographically detected pulmonary artery stiffness in young adult patients presenting with dyspnea

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ABSTRACT

Aims: Vitamin D plays a role in controlling the function of vascular smooth muscle and endothelial cells, even in the pulmonary artery. We hypothesized that pulmonary artery elasticity were comprimised in individuals with relatively low vitamin D levels.

Methods: Adult individuals with the complaint of shortness of breath were enrolled. They were divided into 2 groups according to vitamin D levels, with a cut-off of 20 ng/mL. Pulmonary artery stiffness (PAS) was calculated using the following formula: PAS (kHz/sec) = maximal frequency shift/pulmonary acceleration time. The six-minute walk distance (6MWD) was used to assess the functional exercise capability of subjects.

Results: A total of 71 individuals (male: 31%) were enrolled. Subjects with low vitamin D levels had lower 6MWD than subjects with higher vitamin D levels (443.58±56.20 m vs. 483.20±58.43 m, p=0.007). The PAS was significantly higher in individuals with vitamin D level <20 ng/mL compared with subjects with vitamin D level > 20 ng/mL (11.65±3.76 vs. 9.46±2.53, respectively, p=0.011). Multiple regression showed that vitamin D level was inversely associated with PAS (β=-0.280, p=0.009).

Conclusions: We found that PAS was associated with lower vitamin D levels. Vitamin D deficiency might involved in the dynamics of the pulmonary artery vasculature, even in the absence of significant pulmonary artery pressure elevation.

Introduction

Vitamin D plays a crucial role in developing skeletal function and integrity by controlling calcium homeostasis and bone mineralization. The deficiency of vitamin D is a foremost public health problem worldwide. Its overall incidence is about 30-50% (1), exceeding 50% in some studies (2). Vitamin D has functions other than bone metabolism, and vitamin D deficiency is involved in autoimmune disorders, infectious diseases, inflammatory diseases, metabolic diseases, and certain types of cancer types (3,4). Additionally, recent studies have shown that vitamin D levels are associated with cardiovascular risk factors (age, obesity, diabetes mellitus, chronic kidney disease) and, thereby, may contribute to the development of cardiovascular diseases (5). Nevertheless, low vitamin D levels were associated with significant deterioration in respiratory functions, exercise capacity, and related quality of life (6).

Pulmonary hypertension (PH) is a heterogeneous disorder described by a progressive increase in pulmonary artery pressure and pulmonary vascular resistance leading to right heart failure and reduced cardiac output (7). This hemodynamic definition of PH includes mean pulmonary artery pressure (mPAP) ≥25 mm high, pulmonary capillary wedge pressure ≤15 mm high, and pulmonary vascular resistance greater than or equal to 3 Wood units. Nevertheless, the 6th World Symposium, held in Nice, France, in 2018, suggested taking mPAP >20 mmHg for the definition and treatment of PH (8). While the clinical significance

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of those with PAP >20 mmHg is obvious, it is unclear how the pathophysiology and clinical course are affected in those with shortness of breath and PAP <20 mmHg.

Pulmonary arterial stiffness (PAS) is a novel echo parameter used to guess the pulmonary arterial vasculature's elastic properties. In this technique, the elasticity of the pulmonary artery is computed using a method for defining aortic stiffness (9). Although there are a restricted number of studies investigating the relationship between vitamin D levels and respiratory functions in the literature, there is no study investigating the relationship between PAS and vitamin D levels.

Since vitamin D is involved in the regulation of vascular smooth muscle and endothelial cell functions, we assumed that the elasticity of the pulmonary artery might be disturbed in adults individuals with relatively low levels of vitamin D. Hence, this study aimed to investigate the PAS changes with varying degrees of vitamin D levels in adult individuals with dyspnea but no PH (mPAP <20 mmHg at rest).

Methods

Patient selection

Adult individuals admitted with complaints of shortness of breath and who agreed to participate in this study were enrolled. The baseline demographic, clinical, and biochemical data were obtained from the hospital registry system. Individuals with abnormal hemogram and biochemical parameters (such as anemia, kidney, and liver function abnormalities), coronary artery disease, congenital heart disease, heart failure (ejection fraction below 50%), prominent valvular heart disease, previous history of any heart surgery, atrial fibrillation, diabetes mellitus, hypertension, mPAP higher than 20 mmHg, chronic thromboembolic PH, chronic obstructive pulmonary disease, chronic liver and renal failure, bone mineral disorders, systemic inflammatory disease, and medication may affect vitamin D level were excluded from the study. Also, elderly patients were excluded from this article to avoid the effect of comorbidities and possible vascular aging outcomes on shortness of breath.

We divided 71 individuals into 2 groups according to their vitamin D levels. A 20 ng/mL cut-off of plasma 1,25-dihydroxy vitamin D3 levels was decided. Group 1 consisted of individuals with a 1,25-dihydroxy vitamin D3 <20 ng/mL, while group 2 consisted of individuals with a 1,25-dihydroxy vitamin D3 ≥20 ng/mL.

Echocardiography

We peroformed transthoracic echocardiography using a Vivid S70 ultrasound system (GE Healthcare) using a 3.5 MHz transducer in the left lateral decubitus position at the end of the expiration. Echocardiographic images were saved digitally and analyzed offline by two separate blinded investigators. Echocardiography measurements were obtained according to the standard criteria. Subsequently, the next steps were made to measure PAS. First, pulse-wave Doppler sample volume was placed just 1 cm distal to the pulmonary valve annulus at a speed of 100 mm/sec from the parasternal short axis view and the Doppler flow trace of the pulmonary artery was recorded. Second, Doppler frequency shift, acceleration time (AcT), maximum flow velocity (MFV), and velocity time integral of the pulmonary artery Doppler flow trace were measured. Later, PAS was computed according to the formerly defined formula as the ratio of MFV to pulmonary AcT: PAS (kHz/sec) = MFV/AcT (9).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and Good Clinical Practice/ International Conference on Harmonization and was approved by the Non-Interventional Research Ethics Committee of the University of Health Sciences Türkiye (protocol number: 19/280, date: 25.06.2019). Informed consent was obtained from the participants before enrolling in the study.

Six-minute walk test

The six-minute walk test (6MWT) according to the instructions of the American Thoracic Society is measured to estimate the functional exercise capacity of individuals (10). A suitable hospital corridor was selected for a safe test. Subjects were warned to walk as fast as they could, and a six-minute walking distance (6MWD) was calculated at the end of the test. Also, pulse, respiratory rate, blood pressure, and perceived fatigue on Borg's scale were measured before the test and at the end of the test. Chest pain, severe shortness of breath, dizziness, and sudden pallor was determined as test interruption criteria.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) program for Mac, version 26.0 (Chicago, IL, USA) was used for all statistical analyses and calculations. All the data are transferred to a computer. Numeric variables are presented as means (standard deviation) and categorical variables as percentage values. The distribution of data was assessed graphically and statistically by the Kolmogorov-Smirnov test. For quantitative data with normal distribution Student's t-test was used and the Mann-Whitney U test was used for data without normal distribution. The chi-square test or Fisher's Exact test was used for categorical variables. Pearson's correlation analysis was used for univariate correlation with PAS and, subsequently, a multivariate linear regression model with backward selection was performed to ascertain independent predictors of PAS. A $p < 0.05$ agreed to be statistically significant.

Results

A total of 71 individuals (males: 31%) were enrolled in this study. Group 1 consisted of 46 individuals with a 1,25-dihydroxy vitamin D3 level <20 ng/mL (13 men, 28.3%),

and group 2 consisted of 25 individuals with a 1,25-dihydroxy vitamin D3 level >20 ng/mL (9 men, 36%). There were no significant differences between the study groups concerning the demographic characteristics and laboratory findings (Table 1). During the 6MWT, the average distance achieved by subjects with 1,25-dihydroxy vitamin D3 level <20 ng/mL was lower than subjects with a 1,25-dihydroxy vitamin D3 level >20 ng/mL (443.58±56.20 m vs. 483.20±58.43 m, p=0.007). When we evaluated the individuals according to their smoking status and gender, there was no significant difference between the groups concerning 1,25-dihydroxy vitamin D3 levels and 6DWM (p>0.05 for all).

There was no significant difference between the two groups in terms of conventional echocardiography variables except PAS (Table 2). PAS was considerably increased in individuals

Table 1. Baseline characteristics

	1,25-dihydroxy vit D3 <20 ng/mL (n=46)	1,25-dihydroxy vit D3 ≥20 ng/mL (n=25)	p value
Age, years, mean±SD	28.1±7.5	31.5±8.2	0.083
Male, n (%)	13 (28.3)	9 (36)	0.501
BMI, (kg/m^2), mean±SD	24.39±4.98	24.26±3.76	0.908
Smokers, n (%)	29 (63)	12 (48)	0.384
SBP (mmHg), mean±SD	116.60±12.99	115.64±8.91	0.741
DBP (mmHg), mean±SD	73.28±8.92	75.24±7.82	0.361
Fasting glucose, (mg/dL), mean±SD	92.32±36.14	88.92±14.18	0.653
LDL-C, (mg/dL), mean±SD	106.76±25.15	109.54±30.80	0.686
HDL-C, (mg/dL), mean±SD	50.93±11.91	50.29±10.71	0.825
Total-C, (mg/dL), mean±SD	169.80±46.49	178.45±41.25	0.446
Triglyceride, (mg/dL), mean±SD	118.84±76.50	105.29±44.21	0.427
eGFR (mL/min), mean±SD	101.50±13.54	96.71±25.65	0.306
Hemoglobin (g/dL), mean±SD	13.53±1.43	13.84±1.34	0.393
White blood cell count (10^3/µL), mean±SD	6.83±1.46	6.75±1.64	0.384
Platelet count (10^3/µL), mean±SD	261.58±52.56	243.52±59.86	0.831
1,25-dihydroxy vitamin D3 (ng/mL), mean±SD	11.24±4.77	37.85±16.71	**<0.001**
Calcium (mg/dL), mean±SD	9.40±0.32	9.43±0.43	0.732
Magnesium (mg/dL), mean±SD	1.99±0.14	1.98±0.14	0.785
6MWD (m), mean±SD	443.58±56.20	483.20±58.43	**0.007**

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, eGFR: Estimated glomerular filtration rate, 6MWD: Six-minute walk distance, SD: Standard deviation, vit D3: Vitamin D3, BMI: Body mass index

Table 2. Comparison of echocardiography variables

	1,25-dihydroxy vit D3 <20 ng/mL (n=46)	1,25-dihydroxy vit D3 ≥20 ng/mL (n=25)	p value
LVIDd (mm), mean±SD	42.34±4.87	43.08±4.55	0.539
LVEF (%)	67.52±4.49	66.48±2.98	0.302
IVSd (mm), mean±SD	8.39±1.27	7.88±1.12	0.098
LA (mm), mean±SD	29.45±3.31	29.64±3.38	0.826
Aod (mm), mean±SD	24.78±3.14	25.76±3.39	0.228
Mitral E/A, mean±SD	1.51±0.39	1.50±0.38	0.890
Mitral E/E', mean±SD	5.02±1.97	4.89±2.18	0.799
Tricuspid E/A, mean±SD	1.28±0.32	1.39±0.41	0.227
Tricuspid E/E', mean±SD	4.86±1.56	4.94±1.61	0.854
TAPSE (mm), mean±SD	23.45±2.41	22.40±2.51	0.087
PAS (kHz/sec), mean±SD	11.65±3.76	9.46±2.53	**0.011**

LVIDd: Left ventricular internal diameter end diastole, LVEF: Left ventricular ejection fraction, IVSd: Interventricular septal thickness in diastole, LA: Left atrium, Aod: Aortic root diameter, TAPSE: Tricuspid annular plane systolic excursion, PAS: Pulmonary artery stiffness, SD: Standard deviation, vit D3: Vitamin D3

with 1,25-dihydroxy vitamin D3 level <20 ng/mL compared with subjects with 1,25-dihydroxy vitamin D3 level <20 ng/mL (11.65±3.76 vs. 9.46±2.53, p=0.011) (Table 2). There was a significant correlation between 6MWD, 1,25-dihydroxy vitamin D3, fasting glucose level, hemoglobin level, serum calcium level, and PAS (for 6MWD and PAS r=-0.483, p<0.001; for 1,25-dihydroxy vitamin D3 and PAS r=-0.375, p=0.001; for fasting glucose level and PAS r=0.316, p=0.007; for hemoglobin level and PAS r=-0.266, p=0.025; for serum calcium level and PAS r=-0.303, p=0.010). Also, there was a statistically moderate correlation between 1,25-dihydroxy vitamin D3 level and 6MWD (r=0.339, p=0.004) (Figure 1A-1C). In multiple regression analysis using the backward method entering the independent variables likely to affect the PAS (age, gender, body mass index, systolic blood pressure, estimated glomerular filtration rate, 1,25-dihydroxy vitamin D3, fasting glucose, serum calcium, hemoglobin, 6MWD, mitral EA ratio, tricuspid EA ratio, systolic blood pressure), 1,25-dihydroxy vitamin D3 levels were inversely associated with PAS (β=-0.280, p=0.009). Also, predictors of increased PAS were higher fasting glucose levels (β=0.242, p=0.019) and lower 6MWD (β=-0.293, p=0.010) (Table 3).

Discussion

This study revealed that the pulmonary artery's elastic properties tend to be compromised (as initial vascular alterations) in individuals with low 1,25-dihydroxy vitamin D3 levels.

Vitamin D receptors are present all throughout the human body in several tissue types (11). Since the detection of vitamin D receptors in the cardiovascular system, such as vascular endothelial cells, vascular smooth muscle cells, and cardiac myocytes, there is increasing interest that vitamin D deficiency might be an independent risk factor for cardiovascular and pulmonary disease. Vitamin D may affect the cardiovascular system in a few means. Several pathophysiological pathways have been suggested to explain the relationship between low vitamin D levels and poor cardiovascular function. Vitamin D deficiency may have adverse effects on vascular functions by the expression of inflammatory mediators, such as IL-6, or nuclear factor kβ (12). Low levels of vitamin D have also been associated with endothelial dysfunction, accelerated cellular calcium influx and vascular calcification, smooth muscle proliferation, reduced production of matrix metalloproteinase 2 and 9, increased arterial stiffness and decreased vasoreactivity, expression of LDL receptors on vessels and atherosclerosis, increased oxidative stress, cytokine secretion, thromboembolism, decrease in vascular endothelial growth factor and left ventricular hypertrophy (13-23). Consequently, although it can be said that there is a relationship between vitamin D deficiency and vascular impairment, whether this association is a cause, or a result is still controversial.

Additionally, it has been suggested that vitamin D deficiency has an unfortunate consequence on the pulmonary vascular structure and function, aggravating endothelial dysfunction with reduced NO-dependent relaxation to acetylcholine and increased contractile response to 5-HT (24,25). This situation has been explained by various studies. Downregulation of TASK-1 channels known to be expressed in the lung in pulmonary artery smooth muscle cells, pulmonary endothelial, and epithelial cells is a key event in PH pathogenesis (26,27). Also, in their animal

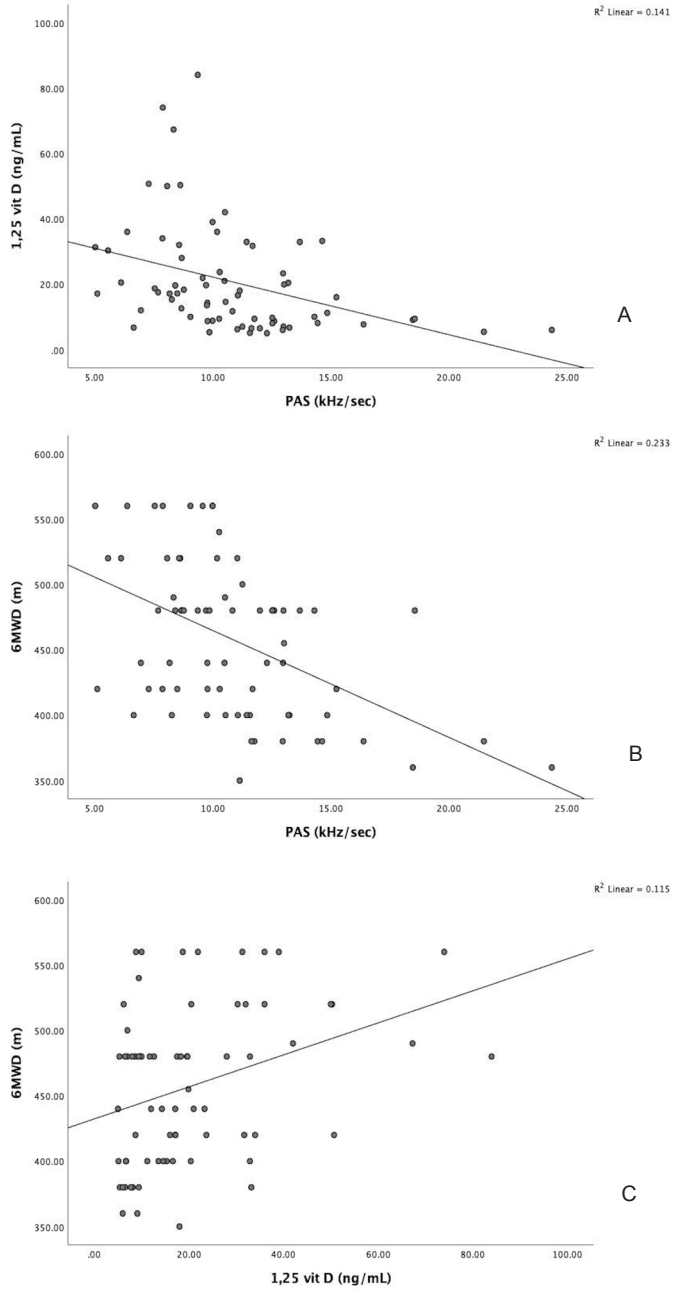

Figure 1. A) Correlations graphs between PAS and 1,25-dihydroxy vitamin D3 level. B) Between PAS and a six-minute walk distance. C) 1,25-dihydroxy vitamin D3 level and six-minute walk distance

PAS: Pulmonary artery stiffness, vit D: Vitamin D, 6MWD: Six-minute walk distance

Table 3. Univariate and multivariate regression analysis based on independent variables likely to affect the pulmonary artery stiffness

Independent variables	Univariate analysis		Multivariate analysis	
	β	p	β	p*
6MWD	-0.483	**<0.001**	-0.293	**0.010**
1,25-dihydroxy vitamin D3	-0.375	**0.001**	-0.280	**0.009**
Fasting glucose	0.316	**0.007**	0.242	**0.019**
Serum calcium	-0.303	**0.010**	-0.116	0.271
Hemoglobin	-0.266	**0.025**	-0.180	0.080

*p-value at the last step in which the independent variables remained in the model.
6MWD: Six-minute walk distance

study, Callejo et al. (24) showed that a vitamin D-free diet caused pulmonary artery muscularization, increased hyperreactivity to 5-HT, worsened endothelial function, reduced TASK-1 currents, decreased KCNK3 mRNA expression and thus a moderate but statically significant increase in mean PAP (24). Furthermore, vitamin D may also act as an endogenous inhibitor of renin biosynthesis, which has been reported as one of the important mechanisms of PH by affecting the concentration of calcium in juxtaglomerular cells (28).

Taken together, it can be considered that a low vitamin D level may induce/accelerate/deteriorate pulmonary artery elastic properties. To the best of our knowledge, there are no studies have examined the role of vitamin D levels in PAS, although there are a limited number of reports about the relationship between vitamin D deficiency and PH. Consequently, bearing in mind this evidence demonstrating the direct effect of vitamin D on the endothelial function and vascular smooth muscle cells, in our study, we examined the different levels of vitamin D on PAS in subjects without PH to delineate the effects of vitamin D on pulmonary vascular structure in detail. Our study is of significance in this aspect. We found that decreased vitamin D level was significantly negatively correlated with PAS in individuals without overt PH.

The description of vitamin D status is debatable, with different levels used throughout the literature. A wide variety of threshold values have been used for vitamin D deficiency, but no definite assumptions have been reached. Generally, a level of 20-30 ng/mL is acceptable to indicate relative vitamin D deficiency and a level >30 ng/L is acceptable to indicate adequate vitamin D (29). For this study, we have considered plasma vitamin D levels <20 ng/mL as a severe deficiency.

Vitamin D replacement therapy is a low-cost treatment method and has no notable adverse effects. While the exact doses and duration of vitamin D are still uncertain, it is important to maintain the circulating vitamin D value >30 ng/mL to observe the beneficial effects on arterial stiffness (16). Although limited data from small clinical studies have shown that vitamin D therapy improves vascular markers such as endothelial function and cardiovascular parameters, it is not exactly known whether it improves pulmonary functions. Higher vitamin D status has been found to be associated with good lung function through an improvement in inspiratory muscle strength and maximum oxygen uptake both in the general population and specifically in patients with chronic obstructive pulmonary disease in whom vitamin D deficiency is also common (30,31). Moreover, Mirdamadi and Moshkdar (6) showed that vitamin D replacement therapy was accompanied by significant improvement in right ventricular size, 6MWD, and mPAP. Although the positive effect of vitamin D treatment on pulmonary functions has been demonstrated, albeit limited, we did not investigate the effects of vitamin D treatment on PAS or other echo parameters in our study. But still, we can speculate that vitamin D deficiency might be considered a modifiable risk factor in individuals with shortness of breath.

Study Limitations

First, the relatively small number of subjects is the main limitation of our single-center study. These might be ambiguous regarding the effect of vitamin D on PAS. Since our study coincided with the Coronavirus disease-2019 outbreak, we could not include the planned number of patients in the study. However, we believe that our findings may inspire further studies to clarify the effect of vitamin D on PAS. Second, since we included adult individuals with atypical complaints, clinically relevant biochemical parameters such as parathyroid hormone level, brain natriuretic peptide level, and inflammatory markers were not studied. Third, there is no agreement about the average range of PAS by this technique. However, our results were consistent with those of previous studies.

Conclusion

In conclusion, in our study, we found that PAS measured echocardiographically might seem to be affected by the low level of vitamin D. The measurement of vitamin D might be used to gain insight into the mechanics of the pulmonary artery vasculature and might be an early marker of pulmonary artery wall's elastic disruption, even in the absence of significant pulmonary artery pressure elevation. Considering the high prevalence of vitamin D deficiency in the general population, care to screen and

treatment of vitamin D deficiency in individuals presenting with shortness of breath is important. Further prospective studies with long-term follow-up periods, preferably randomized controlled trials, must clarify whether vitamin D deficiency is a causal and reversible factor for increased PAS.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Research Ethics Committee of the University of Health Sciences Türkiye (protocol number: 19/280, date: 25.06.2019).

Informed Consent: Informed consent was obtained from all participants before enrolling in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.T., M.Ç., Design: H.T., E.M., Ö.E., S.E., M.Ç., Data Collection or Processing: H.T., M.S.K., O.K., F.B., S.A., Analysis or Interpretation: H.T., E.M., Ö.E., S.E., S.A., Literature Search: Ö.E., O.K., F.B., S.A., Writing: H.T., M.Ç.

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