ORIGINAL ARTICLE

Arterial stiffness parameters associated with vitamin D deficiency and supplementation in patients with normal cardiac functions

Arter sertlik parametreleri kalp fonksiyonları normal olan hastalarda vitamin D eksikliği ve tedavisi ile ilişkilidir

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ABSTRACT

Objective: Arterial stiffness parameters including pulse wave velocity (PWV) and augmentation index (AIx) are associated with increased risk of cardiovascular disease. A close relationship has been demonstrated between vitamin D deficiency and cardiovascular disease. The aim of the present study was to investigate effects of vitamin D deficiency and supplementation on arterial stiffness parameters in patients with normal cardiac functions.

Methods: Study population consisted of 45 patients with vitamin D deficiency and normal cardiac functions. Median age (interquartile range) was 45.0 (12.00) years, and 33 patients were female. Patients were treated with oral administration of vitamin D3. Arterial stiffness parameters were evaluated using Mobil-O-Graph arteriograph system, which detected signals from the brachial artery before and after treatment.

Results: Vitamin D levels significantly increased after treatment (9.0 [6.00] nmol/L vs 29.0 [11.50] nmol/L, p<0.001). No significant difference was observed among conventional echocardiographic parameters before or after treatment. Post-treatment PVW and AIx were significantly lower than baseline measurements (6.8 [1.55] m/s vs 6.4 [1.30] m/s, p<0.001 and 23.0 [22.00]% vs 31.0 [14.50]%, p<0.001, respectively). Baseline vitamin D levels significantly correlated with PWV (r=-0.352, p=0.018). Post-treatment vitamin D levels also significantly correlated with post-treatment PWV (r=-0.442, p=0.002) and AIx (r=-0.419, p=0.004). Multivariate linear regression analysis revealed no independent predictor of baseline log-transformed PWV.

Conclusion: Vitamin D supplementation has beneficial effects on arterial stiffness. Arterial stiffness parameters may aid in the assessment of cardiovascular risk in patients with vitamin D deficiency.

ÖZET

Amaç: Arter sertlik parametrelerinden nabız dalga hızı (NDH) ve artırma indeksi (AIx) artmış kardiyovasküler risk ile ilişkilidir. Önceki çalışmalarda vitamin D eksikliği ve kardiyovasküler hastalık arasında yakın bir ilişki olduğu gösterilmiştir. Çalışmamızın amacı normal kalp fonksiyonları olan hastalarda vitamin D eksikliğinin ve tedavisinin arter sertlik parametreleri üzerine etkisini araştırmaktır.

Yöntemler: Çalışma grubu, vitamin D eksikliği olan, kalp fonksiyonları normal 45 hastadan oluştu. Hastaların ortanca yaşı 45.0 (12.00) yıl idi ve 33'ü kadındı. Hastalar oral vitamin D3 ile tedavi edildi. Arter sertlik parametreleri hastaların tedavi öncesinde ve tedavi sonrasında brakiyal arter akımını saptayan Mobil-O-Graph cihazı kullanılarak değerlendirildi.

Bulgular: Vitamin D seviyeleri hastaların tedavisi sonrasında anlamlı olarak arttı (9.0 [6.00] nmol/L, 29.0 [11.50] nmol/L, p<0.001). Geleneksel ekokardiyografi parametreleri arasında, tedavi öncesi ve sonrasında anlamlı fark yoktu. Tedavi sonrası NDH ve AIx, bazal ölçümlere göre anlamlı olarak daha düşüktü (sırasıyla, 6.8 [1.55] m/s, 6.4 [1.30] m/s, p<0.001 ve 31.0 [14.50] %, 23.0 [22.00] %, p<0.001). Bazal vitamin D seviyesi NDH ile anlamlı ilişki saptandı (r=-0.352, p=0.018). Tedavi sonrası vitamin D seviyesi ile tedavi sonrası NDH (r=-0.442, p=0.002) ve AIx (r=-0.419, p=0.004) arasında anlamlı ilişki saptandı. Çok değişkenli doğrusal regresyon analizinde, dönüştürülmüş bazal NDH'nin bağımsız öngördürücüsü saptanmadı.

Sonuç: Vitamin D tedavisi arter sertlik parametreleri üzerine olumlu etkiler sağlamaktadır. Arter sertlik parametreleri vitamin D eksikliği olan hastalarda kadiyovasküler riskin değerlendirilmesinde klinikçiye yardımcı olabilir.

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Vitamin D deficiency is an important problem affecting 30–50% of the global population.[1] Vitamin D plays a significant role in the regulation of bone metabolism,[2,3] and affects the cardiovascular system by several means, including the renin-angiotensin system, and in several ways, including inflammation, insulin secretion, lipid metabolism, increased adiposity, and blood pressure.[4] Studies have shown that hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), obesity, inflammation, and oxidative stress may contribute to the effects of vitamin D deficiency on the cardiovascular system.[2,5–9] These factors are also associated with endothelial dysfunction and arterial stiffness. Endothelial dysfunction plays an important role in the development of atherosclerosis. A close relationship between atherosclerosis and increased arterial stiffness has been well demonstrated.[10] Studies have shown that vitamin D deficiency is associated with endothelial dysfunction and increased arterial stiffness parameters.[11,12] However, controversy persists regarding possible benefits of vitamin D supplementation on arterial stiffness.[13,14]

The aim of the present study was to evaluate the effects of vitamin D deficiency and supplementation on arterial stiffness parameters in patients with normal cardiac functions.

METHODS

Study population

Fifty-two consecutive patients diagnosed with vitamin D deficiency in the outpatient clinic between January 2014 and March 2014 were enrolled. Diagnosis was based on Endocrine Society guidelines.[15] Patients were evaluated for cardiovascular risk factors including HT, HL, DM, and smoking status. HT was defined as systolic and/or diastolic blood pressure ≥140/90 mmHg, previously diagnosed HT, or use of antihypertensive medications. DM was defined as fasting plasma glucose levels >126 mg/dL at three or more measurements, previously diagnosed DM, or use of anti-diabetic medications such as oral anti-diabetic agents or insulin. HL was defined as serum total cholesterol ≥200 mmol/L, serum triglyceride ≥150 mmol/L, low-density lipoprotein cholesterol ≥130 mmol/L, previously diagnosed HL, or use of lipid-lowering medication. Smoking status was defined as history of tobacco use at admission or up to 6 months prior. Body mass index was calculated by height and weight measurements.

Abbreviations:

AIx	*Augmentation index*
DM	*Diabetes mellitus*
HL	*Hyperlipidemia*
HT	*Hypertension*
PWV	*Pulse wave velocity*

Patients with HT, HL, DM, history of smoking for 6 months or longer, heart failure (ejection fraction <55%), or evidence of coronary artery disease, valvular heart disease, cardiomyopathy, arrhythmia, peripheral arterial disease, active inflammation, active autoimmune disease, chronic renal disease, malignancy, or parathyroid disease were excluded, as were those using calcium or vitamin D supplements, anti-hypertensive, anti-diabetic, or anti-hyperlipidemic drugs, and those who did not attend 3-month follow-up. Patients underwent complete transthoracic echocardiography for evaluation of cardiac functions, and arterial stiffness parameters were assessed with Mobil-O-Graph arteriograph system (IEM GmbH, Stolberg, Germany). Patients were treated with oral administration of 50 000 IU of vitamin D3 per week for 8 weeks, followed by daily maintenance doses of 2000 IU for 4 weeks. All echocardiographic parameters and arterial stiffness parameters were re-evaluated after 12 weeks of therapy. The cardiologist evaluating the echocardiograms and technicians collecting arterial stiffness parameter data were blinded to therapy. The present study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participants.

Conventional transthoracic echocardiography

Conventional transthoracic echocardiography was performed by an experienced cardiologist with a Vivid 7 ultrasound system (GE Vingmed, Horten, Norway). Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. A color Doppler frame scanning rate of 100–140 Hz was used for color track-density imaging and greyscale imaging at a frame rate of 44–82 frames/s. Conventional echocardiographic measurements were performed in accordance with the guidelines of the American Society of Echocardiography.[16]

Assessment of arterial stiffness parameters

Arterial stiffness test was performed with the patient in supine position in a quiet, temperature-controlled room (22–24°C) in the early morning, prior to which

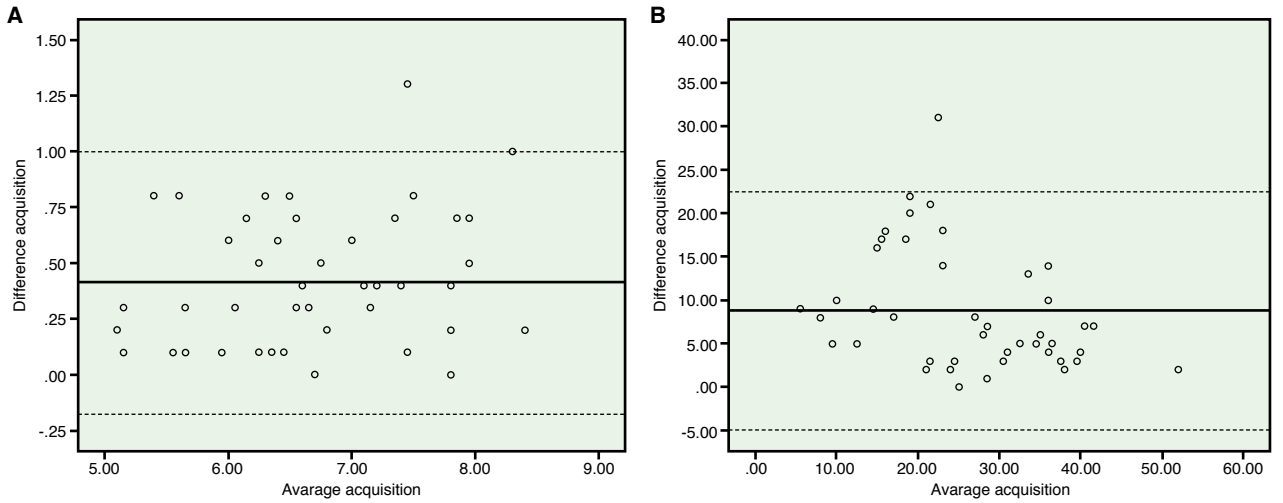

Figure 1. Bland-Altman analysis for pulse wave velocity **(A)** and augmentation index **(B)**.

patients had refrained from eating, or drinking alcohol, coffee, or tea for at least 12 hours. Measurements were performed using a Mobil-O-Graph arteriograph system, which detects signals from the brachial artery with cuff pressure up to up to 35 mm Hg higher than systolic pressure. The basis of this technique is the contraction of the myocardium generating a pulse wave (early systolic peak) that travels down the aorta. The wave is reflected from the aortic wall at the distal branching point, generating a second reflected wave (late systolic peak), the morphology of which depends upon the stiffness of the large artery. Pulse wave velocity (PWV) and augmentation index (AIx), adjusted for a heart rate of 75 bpm, were recalculated according to current guidelines, using the amplitude and time difference of the first and second wave.[17]

Statistical analysis

Statistical analysis was performed with SPSS statistical package for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Whether distribution of continuous variables was normal was determined by Shapiro-Wilk test. Values displaying normal distribution were expressed as mean±SD. Values not displaying normal distribution were expressed as median (interquartile range). Statistical comparison of quantitative data was performed with paired sample t-test for continuous variables displaying normal distribution. Wilcoxon signed-rank test was used for continuous variables not displaying normal distribution. Spearman correlation analysis was performed to determine correlation between vitamin D levels and arterial stiffness parameters. According to results of correlation analysis, a value of $p<0.10$ was considered a potential factor in multivariate analysis. Multivariate linear regression analyses were performed to determine predictors of arterial stiffness parameters. Due to skewed distribution, baseline PWV was log-transformed (ln) for multivariate linear regression analysis. A value of $p<0.05$ was considered statistically significant.

Agreement of PWV and AIx measurements was assessed according to methods described by Bland and Altman. Reproducibility of data obtained by 2 experienced cardiologists was tested. Bland-Altman analysis revealed only minor differences in PWV

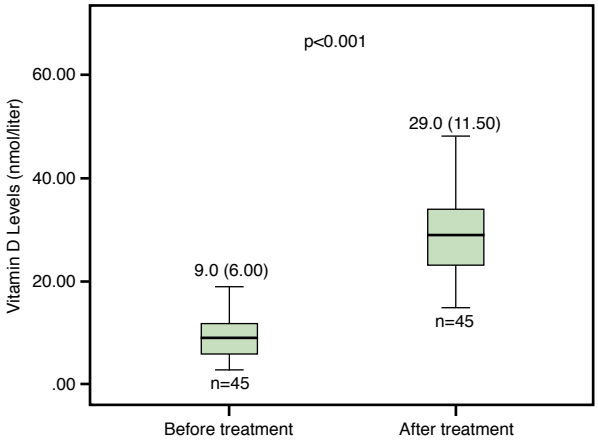

Figure 2. Comparison of vitamin D levels before and after treatment.

(mean: 0.41, +2 SD: 0.998, -2 SD: -0.178) and AIx (mean: 8.80, +2 SD: 22.48, -2 SD: -4.88) (Figure 1).

RESULTS

The study population consisted of 45 patients with vitamin D deficiency, free of cardiovascular risk factors. Median age (interquartile range) was 45.0 (12.00) years, and 33 patients were female. Baseline biochemical parameters are shown in Table 1. Serum calcium, phosphorus, and parathormone levels were within normal range at baseline. Patients were treated with oral administration of 50 000 IU of vitamin D3 per week for 8 weeks, followed by daily maintenance doses of 2000 IU for 4 weeks. Vitamin D levels significantly increased after treatment with standard dose of vitamin D (9.0 [6.00] nmol/L vs 29.0 [11.50] nmol/L, p<0.001; Figure 2). Baseline levels of female patients were significantly lower than those of male patients (7.0 [7.00] nmol/L vs 10.50 [6.80] nmol/L, p=0.023). Conventional echocardiographic parameters are shown in Table 2. No differences were

Table 1. Baseline laboratory findings of study population

Ca / P, (mg/dL)	9.6±0.36 / 3.3±0.55
Parathormone (pg/mL)	42.0 (11.45)
White blood cells / Platelet, (x10^3/μL)	7.3±1.70 / 251.0 (99.50)
Neutrophil / Lymphocyte, (x10^3/μL)	4.1 (1.50) / 2.3±0.66
Hemoglobin, (g/dL) / Hematocrit, (%)	13.1±1.39 / 38.4±3.90
Fasting glucose, (mg/dL)	100.0 (18.00)
Total cholesterol / Triglyceride, (mg/dL)	184.0 (39.00) / 120.0 (86.00)
Low-density lipoprotein / High-density lipoprotein, (mg/dL)	105.0 (32.50) / 46.0 (15.00)
Blood urea nitrogen / Creatinine, (mg/dL)	11.8±2.79 / 0.7±0.14
Na / K, (mEq/L)	140.9±2.58 / 4.2 (0.50)
AST / ALT, (U/L)	16.0 (5.50) / 16.0 (8.00)
TSH, (μIU/mL) / FT4, (ng/dL)	2.1 (1.19) / 1.1 (0.20)

Data are presented as mean±SD or median (interquartile range). Ca: Calcium; Na / K: Sodium / Potassium; AST: Aspartate transaminase; ALT: Alanine transaminase; TSH: Thyrotropin; FT4: Thyroxine.

Table 2. Comparison of two-dimensional transthoracic echocardiographic parameters before and after treatment

	Before treatment (n=45)	After treatment (n=45)	*p*
Left atrial diameter (mm)	33.7±4.13	34.0±3.50	0.479
Left ventricular end-diastolic diameter (mm)	44.5±4.10	45.1±3.75	0.189
Left ventricular end-systolic diameter (mm)	26.8±3.88	26.6±3.36	0.700
Interventricular diameter (mm)	10.0 (2.00)	10.0 (1.00)	0.651
Posterior wall (mm)	9.0 (2.50)	9.0 (2.0)	0.387
Ejection fraction (%)	68.7±6.30	69.8±6.60	0.319
Right atrial area (cm^2)	13.4±3.14	13.1±2.20	0.527
Systolic pulmonary arterial pressure (mmHg)	15.0 (10.00)	20.0 (12.50)	0.067
Tricuspid annular plane systolic excursion (mm)	21.4±3.29	22.2±3.53	0.127
E Velocity (m/s)	0.8±0.18	0.8±0.16	0.846
Left ventricular-e' (cm/s)	12.8±4.01	12.9±3.99	0.216
E/e'	6.6±1.76	6.3±1.91	0.216

Data are presented as mean±SD or median (interquartile range).

Table 3. Comparison of cardiac hemodynamic measurements and arterial stiffness parameters before and after treatment

	Before treatment (n=45)	After treatment (n=45)	*p*
Peripheral systolic blood pressure (mmHg)	128.9±13.41	124.2±15.90	**0.022**
Peripheral diastolic blood pressure (mmHg)	84.0 (14.00)	82.0 (11.50)	0.892
Peripheral pulse pressure (mmHg)	45.0 (19.50)	41.0 (19.00)	**0.011**
Central systolic blood pressure (mmHg)	119.2±12.46	115.6±14.33	0.057
Central diastolic blood pressure (mmHg)	84.5±9.34	84.2±8.76	0.758
Central pulse pressure (mmHg)	31.0 (16.00)	30.0 (14.00)	**0.015**
Cardiac output (l/min)	4.5±0.56	4.3±0.68	0.084
Cardiac index (l/min*1/m²)	2.4 (0.30)	2.3 (0.50)	0.106
Heart rate (beat/min)	81.0 (17.00)	78.0 (18.00)	**0.026**
Body mass index (kg/m²)	28.7±5.17	28.7±5.42	0.867
Pulse wave velocity (m/s)	6.8 (1.55)	6.4 (1.30)	**<0.001**
Augmentation Index (%)	31.0 (14.50)	23.0 (22.00)	**<0.001**

Data are presented as mean±SD or median (interquartile range).
Bold values indicate statistical significance p<0.05.

observed among conventional echocardiographic parameters before and after treatment.

Cardiac hemodynamic parameters were evaluated using Mobil-O-Graph arteriograph and are shown in Table 3. Baseline peripheral systolic blood pressure, heart rate, and peripheral and central pulse pressure were significantly higher than post-treatment measurements. However, all cardiac hemodynamic parameters were within normal range. Arterial stiffness parameters including PWV and AIx were evaluated by oscillometric method before and after treatment of study population. Post-treatment measurements of PVW and AIx were significantly lower than baseline measurements (6.8 [1.5] m/s vs 6.4 [1.30] m/s, p<0.001 and 31.0 [14.50]% vs 23.0 [22.00]%, p<0.001, respectively; Figure 3a, b).

A significant correlation was determined between vitamin D levels and arterial stiffness parameters. Correlation analysis revealed that baseline vitamin D levels were significantly correlated with baseline

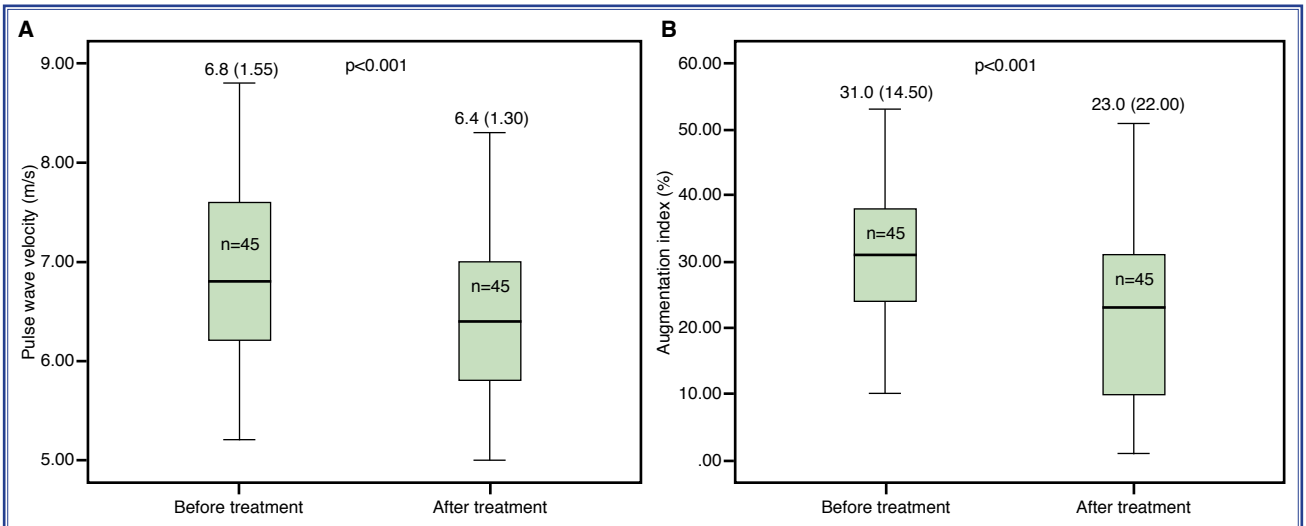

Figure 3. Comparison of pulse wave velocity **(A)** and augmentation index **(B)** before and after treatment.

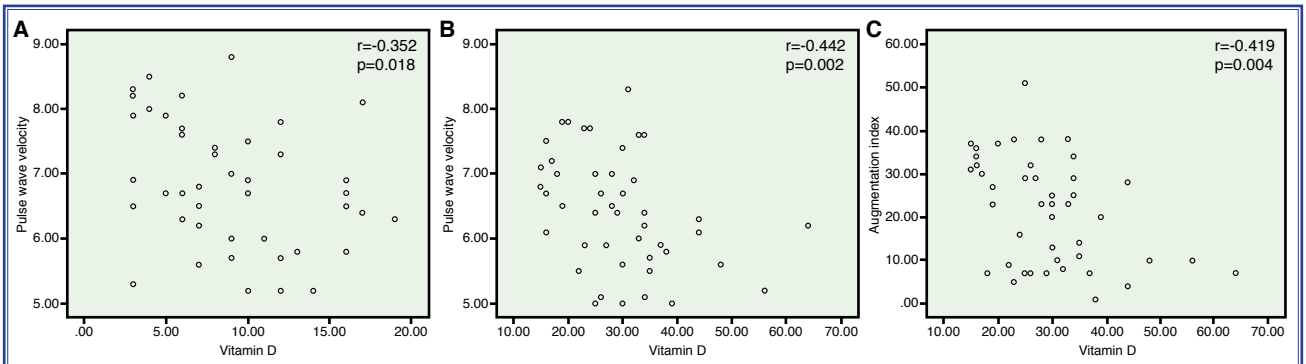

Figure 4. **(A)** Correlation analysis between baseline vitamin D and baseline pulse wave velocity, **(B)** post-treatment vitamin D and post-treatment pulse wave velocity, **(C)** post-treatment vitamin D and post-treatment augmentation index. Aortic stiffness index; PAS: Pulmonary artery stiffness.

PWV (r=-0.352, p=0.018, Figure 4a). Post-treatment vitamin D levels were significantly correlated with post-treatment PWV (r=-0.442, p=0.002, Figure 4b) and AIx (r=-0.419, p=0.004, Figure 4c). Correlation analysis between baseline arterial stiffness parameters and baseline clinical variables is shown in Table 4. A value of p<0.10 was considered a potential factor in multivariate analysis. In correlation analysis, age, tis-

Table 4. Correlation analysis between baseline arterial stiffness parameters and baseline clinical variables

	Pulse wave velocity		Augmentation index	
	r	p	r	p
Calcium level (mg/dL)	0.107	0.484	0.305	0.041
Parathormone level (pg/mL)	0.054	0.727	0.086	0.574
Vitamin D level (nmol/L)	-0.352	0.018	0.141	0.355
Age (years)	0.365	0.014	0.024	0.874
Left ventricular ejection fraction (%)	-0.213	0.160	-0.155	0.311
E/e'	0.256	0.090	0.109	0.476
Peripheral systolic blood pressure (mmHg)	0.370	0.012	0.117	0.443
Peripheral pulse pressure (mmHg)	0.208	0.171	-0.049	0.747
Heart rate (bpm)	0.194	0.202	0.054	0.724
Body mass index (kg/m²)	0.210	0.167	0.237	0.117

Bold values indicate statistical significance p<0.1. Correlation analysis was performed using Spearman correlation test for all parameters.

Table 5. Multivariate linear regression analysis to determine independent predictors of log-transformed pulse wave velocity

	Log-transformed pulse wave velocity		
	β	95% confidence interval for β	p
Vitamin D level	-0.256	-0.017 – 0.001	0.073
E/e'	0.125	-0.017 – 0.037	0.452
Age	0.150	-0.003 – 0.008	0.360
Peripheral systolic blood pressure	0.254	<0.001 – 0.006	0.088

Because of the skewed distribution of baseline pulse wave velocity, this variable was log-transformed for multiple linear regression analysis.

sue Doppler E/e' ratio, peripheral systolic blood pressure, and vitamin D level were potential predictors of baseline PWV. Multivariate linear regression analysis was performed to determine independent predictors of baseline ln PWV. No independent predictor of baseline ln PWV was determined in multivariate analysis among age, E/e', peripheral systolic blood pressure, and vitamin D level, factors included in the linear regression model (Table 5).

DISCUSSION

The present study demonstrated that vitamin D supplementation provided beneficial effects on arterial stiffness parameters in patients with normal cardiac functions. Level of vitamin D was correlated with arterial stiffness parameters.

Arterial stiffness was defined as the sum of distensibility, compliance, and elasticity of the vascular system. Several devices including high-fidelity applanation tonometers, Doppler probes, and oscillometric devices have been used to assess arterial stiffness.[18] Assessment of arterial stiffness using mechanotransducers, applanation tonometers, or Doppler probes requires an expert operator. These methods are time-consuming, and reproducibility is limited. However, the oscillometric method is a non-invasive, reliable, reproducible, and easy method of evaluating arterial stiffness parameters in clinical practice. Arterial stiffness parameters have been used as a surrogate marker of increased cardiovascular risk in several diseases.[10,19–21] Parameters including PWV and AIx have provided additive benefits over traditional cardiovascular risk scores to identify patients with high cardiovascular risk.

It has been demonstrated by several methods that vitamin D has a beneficial effect on arterial stiffness. However, controversy persists. While some studies have demonstrated beneficial effects,[12,22] others have reported adverse effects on vascular functions.[13,14,23] Giallauria et al. reported that vitamin D levels were inversely associated with increased arterial stiffness in a normative aging population, irrespective of traditional risk factor burden (adjusted r2=0.27; β=-0.43; p=0.001).[12] Watson et al. reported that 1,25-vitamin D levels were inversely correlated with vascular calcification.[22] However, Ryu et al. suggested that vitamin D levels produced no beneficial effects on arterial stiffness or cardiovascular risk in patients with type 2 diabetes.[13] Chitalia et al. assessed flow-mediated dilatation, PWV, AIx, and endothelial biomarkers in patients with non-diabetic chronic kidney disease before and after vitamin D treatment.[14] Although flow-mediated dilatation improved from 3.1±3.30% to 6.1±3.70% (p=0.001), PWV and AIx remained unchanged.

Vitamin D has been shown to increase endothelial nitric oxide levels, inhibit platelet-leukocyte aggregation and pro-inflammatory cytokines, affect vascular muscle tone, and regulate immune response, serving a protective role. A possible explanation of negative effects on arterial stiffness parameters concerns the association between vitamin D and increased vascular calcification. It has been proposed that arterial calcification increases risk of cardiovascular disease, irrespective of presence of conventional risk factors.[23] Vitamin D also has favorable effects on arterial stiffness due to its effects on the renin-angiotensin system, inhibition of pro-inflammatory cytokines, and regulation of lipid metabolism.

The present study demonstrated that vitamin D supplementation provides favorable effects on arterial stiffness parameters. Although cardiac hemodynamic parameters were within normal range at baseline and after treatment, peripheral systolic blood pressure, pulse pressure, and heart rate were higher at baseline, compared to post-treatment, which may explain the positive effect on arterial stiffness. While coronary calcification is a process that requires time, follow-up period was only 3 months. Negative effects of vitamin D on arterial stiffness may be obscured by insufficient follow-up duration.

Study limitations

The present study was limited by relatively small sample size. While design was prospective, data was obtained only at baseline and 3 months after treatment. Were duration of follow-up longer, prognostic data could have been obtained. The present study could be improved by the inclusion of a control group treated with a placebo. Further prospective, large-scale clinical trials are warranted to validate results.

Conclusion

Vitamin D supplementation has beneficial effects on arterial stiffness parameters in patients with vitamin

D deficiency. Level of vitamin D is significantly correlated with arterial stiffness parameters, which may aid in the assessment of cardiovascular risk in patients with vitamin D deficiency.

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Keywords: Arterial stiffness; augmentation index; cardiovascular risk; pulse wave velocity; vitamin D.

Anahtar sözcükler: Arteryel sertlik; artırma indeksi; kardiyovasküler risk; nabız dalga hızı; vitamin D.