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The relationship between vitamin D deficiency and hypertensive organ damage

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ABSTRACT

Aim: In this study, we aimed to examine the relationship between vitamin D level and target organ damage (TOD) in primary hypertension patients by eliminating the effects of hypertension duration and antihypertensive treatments.

Material and Method: The study included 144 patients with primary hypertension. Vitamin D levels were classified as sufficiency (VDS), deficiency (VDD), and severe deficiency (VDSD). In case of more than one TOD indicator (microalbuminuria or proteinuria, left ventricular mass index and carotid intima-media thickness), it was considered as multi organ involvement (OI). In the multiple regression model, besides the traditional risk factors, the effects of hypertension duration and anti-hypertensive treatments were adjusted.

Results: The rates of VDS and VDD were lower in TOD (+) compared to TOD (-) (14.1% vs 51.5%, 32.1% vs 42.4%; p<0.001), while VDSD ratio was higher (53.8% vs 6.1%, p<0.001). VDSD ratio was higher in hypertensive patients with single-OI compared to TOD (-), while its was higher in patients with multi-OI compared to single-IO. In the multivariable regression model; showed that 1 ng/mL decrease in the Vitamin D increased the probability of TOD by 1.22 folds [vs TOD (-)], probability of single organ involvement by 1.19 folds [vs TOD (-)], and probability of multi-IO by 1.11 folds (vs single-IO).

Conclusion: In hypertensive patients, a decrease in vitamin D levels is associated with an increase in TOD indicators. The risk of developing TOD and multi-IO is higher in vitamin D deficiency. Vitamin D supplements may be beneficial in hypertensive organ damage, regardless of disease duration and anti-hypertensive treatments.

Keywords: Atherosclerosis, hypertension, vitamin D, target organ damage

INTRODUCTION

Vitamin D deficiency and hypertension, which are globally common public health problems, are important risk factors for cardiovascular events (1). It has been suggested that a decrease in Vitamin D levels increases blood pressure (BP) levels and may be a new risk factor in causing hypertension. (2, 3). Atherosclerosis due to cardiac and vascular tissue damage caused by high BP causes target organ damage (TOD) (4). Therefore, Vitamin D has been suggested as an important mechanism in hypertensive organ damage (5).

Organs and tissues containing vitamin D receptors, such as the heart, kidneys, and vascular endothelium, can affect renin-angiotensin system (RAAS) activation (6). This may cause endothelial or renal dysfunctions in hypertensive patients (7).The incidence of endothelial dysfunction and cardiac hypertrophy was higher in hypertensive patients with VDD (8). Previous studies have shown an inverse correlation between the Vitamin D levels and subclinical TOD indicators (carotid intima-media thickness (CIMT), left ventricular mass index (LVMI) and microalbuminuria) in hypertensive patients (9, 10). In an experimental study in rats, vitamin D depletion was shown to increase creatinine levels and affect RAAS components that may directly contribute to hypertensive organ damage (5). On the other hand, there was a positive correlation between duration of hypertension and incidence of VDD (11). However, it is unknown whether VDD in hypertension is a cause of disease or an epiphenomenon.

We hypothesized that there might be a negative correlation between duration of hypertension and multi-organ involvement and Vitamin D levels. In this study, we aimed to examine the relationship between vitamin D level and hypertensive organ damage in primary hypertension patients by eliminating the effects of hypertension duration and antihypertensive treatments.

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MATERIAL AND METHOD

This retrospective study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

In this study, 618 patients who were followed up with the diagnosis of hypertension in the Cardiology Clinic from January 2021 to January 2022 were evaluated. The inclusion criteria of the study were patients aged 18 years to 65 years, with documented levels of vitamin D, microalbuminuria or proteinuria, LVMI and CIMT. The exclusion criteria were secondary hypertension, history of diabetes mellitus, asthma, chronic obstructive lung disease, rheumatic diseases, coronary artery disease, malignancy, active or chronic infections, acute or chronic kidney disease, peripheral artery disease, cerebrovascular disease, liver diseases, heart failure, presence of proteinuria at nephrotic level, patients without documented vitamin D levels, and patients without documented levels of TOD markers (microalbuminuria or proteinuria, LVMI and CIMT). Previous studies have reported a higher incidence of vitamin D deficiency in geriatric patients (aged 65 years and older) and hypertension duration of 8 years or more (11, 12). In order to avoid the bias of vitamin D deficiency, we also excluded patients in this group. A total of 474 patients with exclusion criteria were excluded from the study. Finally, 144 patients were included in the analysis.

Study Protocol

The diagnosis of hypertension was evaluated according to the 2018 ESC criteria (13), and its was defined as systolic BP (SBP) of ≥140 mmHg and diastolic BP (DBP) of ≥90 mmHg.

Microalbuminuria of >30 mg/day or proteinuria of >150 mg/day, LVMI of >95 g/m2 in women and >115 g/m2 in men, and CIMT of >0.9 mm or presence of plaque in the carotid were as the presence of TOD (14). According to these findings, the patients were divided into 2 groups as those with and without TOD and patients with more than single of the TOD indicators were evaluated as subclinical multi-organ involvement. In addition, patients were divided into 3 groups according to their vitamin D levels as follows: sufficiency ≥20 ng/mL (VDS), deficiency 10-19 ng/mL (VDD), and severe deficiency <10 ng/mL (VDSD) (15).

Demographic and laboratory data were obtained by accessing patient files through the hospital's electronic information system.

Laboratory Testing

Erythrocytes and thrombocytes were performed by impedance method, leukocytes were performed by optical laser scattering (light scattering), and other complete blood count parameters were measured with a Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Microalbuminuria and proteinuria in 24 hours (by turbidimetric methods) and lipid parameters (by enzymatic colorimetric methods) were performed with a Hitachi Modular P800 autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Hemoglobin was measured photometrically. Inflammatory indices were obtained from the complete blood count as follows: neutrophil to lymphocyte ratio (NLR) = neutrophil count / lymphocyte count, platelet to lymphocyte ratio (PLR) = platelet count / lymphocyte count.

The 25-hydroxyvitamin D, which the major circulating form of vitamin D, levels were measured by radioimmunassay method (Beckman Coulter, Indianapolis, USA) in an autoanalyzer.

Echocardiographic Examination

Echocardiographic measurements were made with an echocardiography device (2.5 MHz transducer, Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway) by a blinded cardiologist. Left ventricular mass (LVM) was calculated using the Devereux formula (LVM = 1.04 × [(IVST + PWT + LVDd)3 – (LVDd)3] – 13.6) and was indexed to body surface area (16). LVMI of >95 g/m2 in women and >115 g/m2 in men were considered left ventricular hypertrophy

Carotid Ultrasonography

CIMT measurements, with the patient in the supine position and both hands under the head, were measured with a high-resolution B-mode device (Logiq 7, GE Med Inc., Chicago, IL, USA) by a radiologist blinded to the study. An automated linear probe was used for measurements from the right and left common carotid arteries. Measurements were performed at 3 points: the right carotid artery branches from the brachiocephalic trunk, the left carotid arteries from the aorta at 2 cm away, and the bifurcation of the internal carotid arteries. Longitudinal measurements were performed from distances of media-adventitia echogenicity and vessel lumen echogenicity. CIMT was calculated by taking the average of 3 measurements made for each carotid artery.

The presence of plaque was defined according to the Mannheim consensus (17). The criteria were defined as follows: a focal protrusion in the lumen measuring at least cIMT >1.5 mm; a protrusion at least 50% greater than the surrounding cIMT; or an arterial lumen encroaching >0.5 mm.

Statistical Analysis

SPSS 20 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. To determine whether or not data were normally distributed, Kolmogorov-Smirnov testing was applied. While numerical variables are given as mean ± standard deviation or median (min-max), and categorical values are given as numbers and percentages. Chi-square and Fisher's exact testing was applied to compare categorical data. Student T test or Mann-Whitney U test was used in the comparison of numerical variables in two groups according to normality distribution. ANOVA test (post hoc: Bonferroni test) or Kruskall Wallis H test (post hoc: Dunn's test) was used to compare numerical variables between Vitamin D groups and hypertensive organ involment groups according to normality distribution. Spearman correlation analysis was used for the relationship between Vitamin D and other numerical parameters. Independent predictors of TOD were determined by logistic regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 54.7±10.8 years and the mostly of them were female (63.9%). Vitamin D was sufficient in 31.3% of hypertensive patients, while it was deficient in 36.8% and severely deficient in 31.9%. Mean SBP levels, mean DBP levels, mean NLR levels were higher in VDSD group compared to the other groups. The levels of TOD indicators were higher in VDSD group compared other groups, while its were higher in VDD group compared to the VDS group (**Table 1**). The relationship between vitamin D levels and BP levels and TOD indicators is shown in **Figure 1**. A negative correlation was found between vitamin D levels and CRP levels (r= -0.305; p=0.018) and neutrophil levels (r= -0.335; p=0.005) and NLR levels (r= -0.340; p=0.004).

Table 1. Demographic and laboratory findings according to Vitamin D status in hypertension patients

Variables	All population n=144	Vitamin D			p
		Sufficiency n=45	Deficiency n=53	Severe deficiency n=46	
Demographic findings					
Age, years	53.7±10.8	54.1±9.8	53.7±11.9	53.2±10.4	0.449
Female gender, n (%)	92(63.9)	27(60.0)	31(58.5)	34(73.9)	0.230
BMI, kg/m2	30.4±5.1	29.8±4.8	29.9±5.3	31.7±5	0.118
Smoking, n (%)					0.670
Non-smoker	96(66.7)	33(73.3)	34(64.2)	29(63.0)	
Smoker	30(20.8)	6(13.3)	13(24.5)	11(23.9)	
Ex-smoker	18(12.5)	6(13.3)	6(11.3)	6(13.0)	
Alcohol use, n (%)	33(22.9)	10(22.2)	10(18.9)	13(28.3)	0.510
DoH, years	3(2-5)	2(2-5)	3(2-5)	4(2-6)	0.384
Drugs, n (%)					
ACEI/ARBs	74(51.4)	24(53.3)	29(54.7)	21(45.7)	0.646
Beta blocker	22(15.3)	6(13.3)	8(15.1)	8(17.4)	0.918
CCB	64(44.4)	20(44.4)	20(37.7)	24(52.2)	0.372
Diuretics	45(31.5)	17(38.6)	16(30.2)	12(26.1)	0.441
SBP, mm Hg	136.7±22.4	128.0±19.5	133.0±21.5	149.4±20.7	<0.001*
DBP, mm Hg	84.3±13.9	80.0±12.4	80.2±12.7	93.0±12.7	<0.001*
Laboratory findings					
Microalbuminuria, g/24h	11.4(5.4-20.8)	7.1(4.5-14)	9.2(4.8-19)	18.3(12.2-32.7)	<0.001*
Proteinuria, g/24h	92(67.9-144.1)	73.3(54-93.3)	100.4(70.2-135.6)	132.6(84-176)	<0.001*
LVMI, g/m2	93.4±17.6	84.8±17.2	93.2±15.4	104.4±17.7	<0.001*
CIMT, mm	0.9±0.2	0.8±0.1	0.9±0.2	1.0±0.2	<0.001*
WBC, x109/L	7.5±2.3	7.4±1.5	7.4±2.2	7.6±2.5	0.847
Neutrophil, x109/L	4.7±1.4	4.4±1.2	4.4±1.4	5.3±1.5	0.002*
Platelet, x109/L	304.4±63.7	301.2±57.4	309.8±67.7	301.3±65.8	0.741
Lymphocyte, x109/L	2.2±0.7	2.2±0.6	2.3±0.9	2.2±0.6	0.723
NLR	2.3±0.7	2.1±0.7	2.1±0.8	2.5±0.7	0.008*
PLR	146.5±38.2	143.7±35.5	149.2±43.9	146.2±36.5	0.822
FBG, mg/dL	96.8±14.4	96.6±11.5	94.1±11.8	100.1±18.6	0.123
Hemoglobin, g/dL	13.9±1.5	13.9±1.4	13.9±1.4	13.9±1.6	0.964
Total cholestrol, mg/dL	202.5±42.5	200.5±46.2	211.7±32.4	194.1±47.3	0.120
LDL, mg/dL	121.5±36.4	118.9±38	130.2±29.4	114.2±40.7	0.084
HDL, mg/dL	50.5±13.3	51.4±12.3	50.6±13.7	49.3±14	0.748
Triglyceride, mg/dL	136(97-196)	136(100-196)	138(94-196)	125(97-200)	0.903
Albumin, g/dL	4.6±0.4	4.6±0.3	4.6±0.4	4.5±0.3	0.418
CRP, mg/dL	3.5(2-6.3)	2.7(2-5.1)	4(2.1-6.6)	3.8(1.8-7.6)	0.560
Vitamin D, ng/mL	15.1(9.6-21.6)	24.9(22.2-28.1)	15.2(12.9-18.3)	7.2(5.6-9.3)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as number (%). * p < 0.05 shows statistical significance. Bold characters differ between groups (post-hoc: Bonferroni or Dunn's test) Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers, CIMT, carotid intima media thickness; CRP, C – reactive protein; DBP, diastolic blood pressure; DoH, duration of hypertension; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; LVMI, left ventricular mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

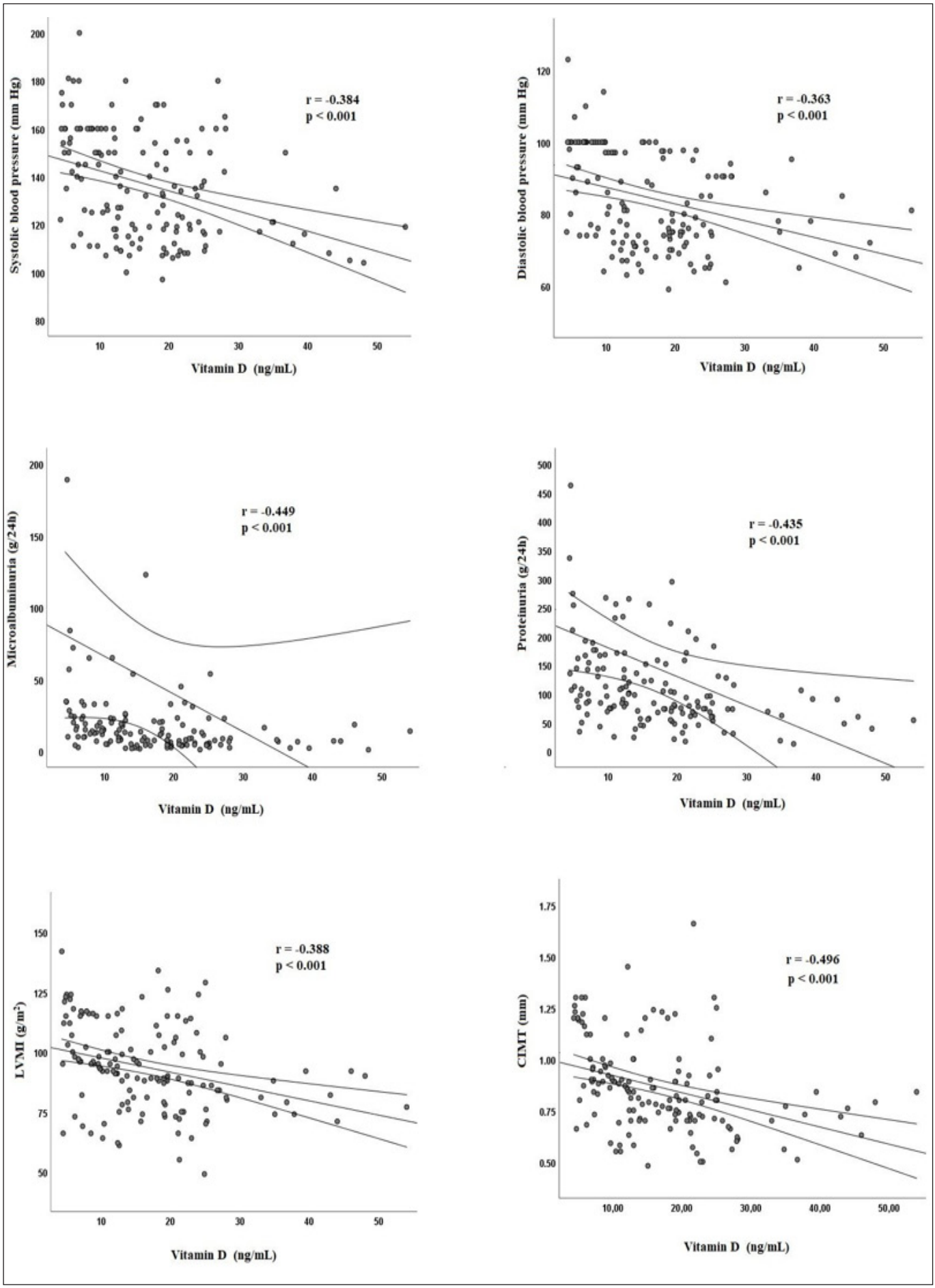

Figure 1. Scatter plot representation of the negative correlation between levels of vitamin D, blood pressure and TOD indicators

Mean NLR, mean PLR, and median CRP levels were higher in TOD (+) compared to TOD (-), while median Vitamin D level was lower (10 vs 20.7 ng/mL, p<0.001) (**Table 2**). Mean NLR, mean PLR, and median CRP levels were higher in hypertensive patients with single-organ involvement compared to TOD (-), while median Vitamin D level was lower (**Table 3**). In addition, mean NLR and median CRP levels were higher in hypertensive patients with mutli-organ involvement compared to single-organ involvement, while median Vitamin D levels were lower (**Table 3**).

Table 2. Demographic and laboratory findings according to presence of target organ damage in hypertension patients

Variables	Target Organ Damage		p
	No n=66	Yes n=78	
Demographic findings			
Age, years	55.2±10.7	54.3±10.9	0.563
Female gender, n (%)	39 (59.1)	53 (67.9)	0.299
BMI, kg/m2	29.6±5.2	31.1±5.0	0.077
Smoking, n (%)			0.815
Non-smoker	42 (63.6)	54 (69.2)	
Smoker	15 (22.7)	15 (19.2)	
Ex-smoker	9 (13.6)	9 (11.5)	
Alcohol use, n (%)	13 (19.7)	20 (25.6)	0.432
DoH, years	2 (2-5)	3.5 (2-6)	0.180
Drugs, n (%)			
ACEI/ARBs	39 (59.1)	35 (44.9)	0.089
Beta blocker	9 (13.6)	13 (16.7)	0.650
CCB	25 (37.9)	39 (50.0)	0.179
Diuretics	22 (33.8)	23 (29.5)	0.592
SBP, mm Hg	133.4±22.4	139.5±22.1	0.104
DBP, mm Hg	82.5±13.4	85.7±14.2	0.168
Laboratory findings			
Microalbuminuria, g/24h	6.8 (4.4-9)	19.5 (10.9-32.7)	<0.001*
Proteinuria, g/24h	69.8 (52-90.8)	138.8 (84-188.7)	<0.001*
LVMI, g/m2	84.2±11.9	101.2±18	<0.001*
CIMT, mm	0.7±0.1	1.0±0.2	<0.001*
WBC, x109/L	7.0±1.7	7.9±2.7	0.015*
Neutrophil, x109/L	4.0±0.9	5.3±1.5	<0.001*
Platelet, x109/L	284.1±54.6	321.6±66.1	<0.001*
Lymphocyte, x109/L	2.3±0.8	2.2±0.7	0.547
NLR	1.9±0.4	2.6±0.7	<0.001*
PLR	133.8±33.1	157.3±42.8	<0.001*
FBG, mg/dL	96.5±13.9	97±14.8	0.843
Hemoglobin, g/dL	14±1.4	13.8±1.6	0.320
Total cholestrol, mg/dL	199.2±37.4	205.4±46.6	0.385
LDL, mg/dL	119±32.2	123.7±39.9	0.450
HDL, mg/dL	49.3±13.6	51.5±13	0.347
Triglyceride, mg/dL	138 (97-188)	129 (96-201)	0.885
Albumin, g/dL	4.6±0.4	4.5±0.3	0.475
CRP, mg/dL	2.6 (1.6-5.4)	4.5 (2.6-6.9)	0.009*
Vitamin D, ng/mL	20.7 (14.6-26.7)	10 (7-17.9)	<0.001*
Sufficiency, n (%)	34 (51.5)	11 (14.1)	<0.001*
Deficiency, n (%)	28 (42.4)	25 (32.1)	<0.001*
Severe deficiency, n (%)	4 (6.1)	42 (53.8)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as number (%). * p < 0.05 shows statistical significance. Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers, CIMT, carotid intima media thickness; CRP, C – reactive protein; DBP, diastolic blood pressure; DoH, duration of hypertension; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; LVMI, left ventricular mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

The rates of VDS and VDD were lower in TOD (+) compared to TOD (-) (14.1% vs 51.5%, 32.1% vs 42.4%; p<0.001), while VDSD ratio was higher (53.8% vs 6.1%, p<0.001) (**Table 2**). VDSD ratio was higher in hypertensive patients with single organ involvement compared to TOD (-), while its was higher in patients with multi-organ involvement compared to single-organ involvement (**Figure 2**) (**Table 3**).

In the multivariable regression model, increased NLR levels and decreased Vitamin D were determined as common independent predictors of the presence of TOD and single organ involvement. Independent predictors of multi-organ involvement were found to be increased SBP, increased NLR levels and decreased Vitamin D levels. According to this; it was determined that 1 ng/mL decrease in the Vitamin D increased the probability of TOD by 1.22 folds [TOD (-)], probability of single organ involvement by 1.19 folds [vs TOD (-)], and probability of multi-organ involvement by 1.11 folds (vs single organ involvement) (**Table 4**).

Table 4. Independent predictors for presence of target organ damage and multi-organ involvement

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
TOD (+) (ref: TOD(-))						
WBC	1.22	1.03-1.44	0.019*	-	-	-
Neutrophil	2.44	1.69-3.54	<0.001*	-	-	-
Platelet	1.02	1.01-1.03	0.001*	-	-	-
NLR	8.61	3.67-20.21	<0.001*	10.22	3.51-29.82	<0.001*
PLR	1.02	1.01-1.03	<0.001*	-	-	-
CRP	1.03	1.01-1.07	0.012*	-	-	-
Vitamin D	0.84	0.78-0.89	<0.001*	0.81	0.74-0.88	<0.001*
Nagelkerke R2= 0.628, p< 0.001						
Single OI (ref: TOD(-))						
WBC	1.24	1.02-1.58	0.047*	-	-	-
Neutrophil	2.14	1.37-3.34	0.001*	-	-	-
Platelet	1.03	1.01-1.07	0.018*	-	-	-
NLR	8.06	2.77-23.45	<0.001*	9.41	2.66-33.25	<0.001*
PLR	1.02	1.01-1.03	0.027*	-	-	-
CRP	1.02	1.01-1.04	0.036*	-	-	-
Vitamin D	0.85	0.78-0.93	<0.001*	0.84	0.76-0.92	<0.001*
Nagelkerke R2= 0.497, p< 0.001						
Multi OI (ref: One OI)						
SBP	1.04	1.01-1.06	0.003*	1.03	1.01-1.06	0.009*
DBP	1.05	1.02-1.09	0.005*	-	-	-
Neutrophil	1.44	1.03-2.02	0.032*	-	-	-
NLR	2.25	1.17-4.35	0.003*	1.98	1.08-4.01	0.041*
CRP	1.04	1.01-1.08	0.046*	-	-	-
Vitamin D	0.92	0.85-0.99	0.030*	0.90	0.86-0.95	0.033*
Nagelkerke R2= 0.412, p< 0.001						

In the multivariable regression analysis, the effects of age, gender, duration of hypertension, and drug use were adjusted. * p < 0.05 shows statistical significance. Abbreviations: CI: confidence interval; CRP, C – reactive protein; DBP, diastolic blood pressure; NLR, neutrophil to lymphocyte ratio; OR: odds ratio; OI: organ involvement; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

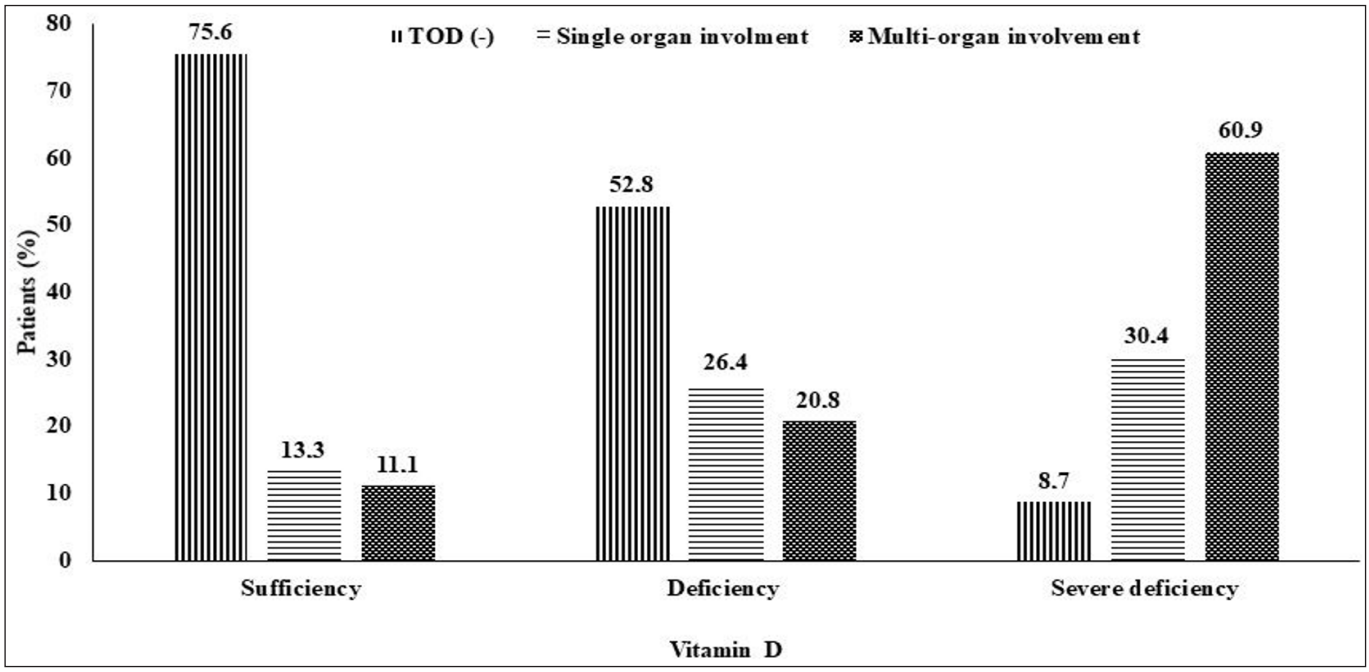

Figure 2. Distribution of hypertensive organ involvement according to vitamin D deficiency

Table 3. Demographic and laboratory findings according to organ involvement in hypertension patients

Variables	Target Organ Damage (-) n=66	Target Organ Damage (+)		p
		Single IO n=34	Multi IO n=44	
Demographic findings				
Age, years	55.2±10.7	54.7±9.8	54.0±11.6	0.465
Female gender, n (%)	39 (59.1)	22 (64.7)	31 (70.5)	0.487
BMI, kg/m2	29.6±5.2	30.8±3.7	31.4±5.8	0.179
Smoking, n (%)				0.971
Non-smoker	42 (63.6)	23 (67.6)	31 (70.5)	
Smoker	15 (22.7)	7 (20.6)	8 (18.2)	
Ex-smoker	9 (13.6)	4 (11.8)	5 (11.4)	
Alcohol use, n (%)	13 (19.7)	8 (23.5)	12 (27.3)	0.625
DoH, years	2 (2-5)	2.5 (2-6)	4 (2-6)	0.199
Drugs, n(%)				
ACEI/ARBs	39 (59.1)	13 (38.2)	22 (50.0)	0.149
Beta blocker	9 (13.6)	5 (14.7)	8 (18.2)	0.805
CCB	25 (37.9)	18 (52.9)	21 (47.7)	0.327
Diuretics	22 (33.8)	11 (32.4)	12 (27.3)	0.803
SBP, mm Hg	133.4±22.4	130.6±20.8	146.3±20.8	0.002*
DBP, mm Hg	82.5±13.4	80.4±13.3	89.8±13.7	0.004*
Laboratory findings				
Microalbuminuria, g/24h	6.8 (4.4-9)	14.8 (8-24.8)	20.8 (13-34.5)	<0.001*
Proteinuria, g/24h	69.8 (52-90.8)	103 (75.1-171)	158.1 (101.2-201.3)	<0.001*
LVMI, g/m2	84.2±11.9	94.4±19.3	106.5±15.1	<0.001*
CIMT, mm	0.7±0.1	0.9±0.2	1.1±0.2	<0.001*
WBC, x109/L	7.0±1.7	7.8±1.9	8.0±3.2	0.029*
Neutrophil, x109/L	4.0±0.9	4.8±1.1	5.8±1.6	<0.001*
Platelet, x109/L	284.1±54.6	315.6±68.2	326.2±64.8	0.001*
Lymphocyte, x109/L	2.3±0.8	2.2±0.7	2.2±0.7	0.831
FBG, mg/dL	96.5±13.9	95.9±10.6	97.9±17.6	0.810
Hemoglobin, g/dL	14.0±1.4	13.8±1.6	13.7±1.5	0.589
Total cholestrol, mg/dL	199.2±37.4	203.4±56.2	207.2±37.4	0.637
LDL, mg/dL	119.0±32.2	118.4±46.7	128.0±33.1	0.394
HDL, mg/dL	49.3±13.6	49.6±12.8	53.0±13.2	0.350
Triglyceride, mg/dL	138 (97-188)	137.5 (107-218)	121 (94-158)	0.318
Albumin, g/dL	4.6±0.4	4.6±0.2	4.5±0.4	0.301
CRP, mg/dL	2.6 (1.6-5.4)	4.0 (1.8-6.4)	5.3 (2.1-8.0)	0.028*
Vitamin D, ng/mL	20.7 (14.6-26.7)	12.6 (8.8-19.2)	8.5 (5.9-14.8)	<0.001*
Sufficiency, n (%)	34 (51.5)	6 (17.6)	5 (11.4)	<0.001*
Deficiency, n (%)	28 (42.4)	14 (41.2)	11 (25.0)	<0.001*
Severe deficiency, n (%)	4 (6.1)	14 (41.2)	28 (63.6)	<0.001*

DISCUSSION

In this study, a negative correlation was found between levels of TOD indicators and Vitamin D in hypertensive patients. The levels of TOD indicators increased gradually from VDD to VDSD, while the risk of multi-organ involvement was higher in patients with VDSD. In addition, a decreased Vitamin D level was found to be an independent predictor of both presence of TOD and multi-organ involvement. This association was independent of disease duration and anti-hypertensive treatment. These findings indicate that the risk of TOD may be higher in hypertensive patients with VDD or VDSD.

We found a negative correlation between blood pressure and Vitamin D levels in hypertensive patients. Vitamin D has a cardiovascular protective effect by taking part in the modulation of inflammatory cytokines and RAAS (18). This role of vitamin D can affect BP levels and cause an inverse relationship. In previous studies, it has been shown that a 1 ng/mL decrease in Vitamin D levels causes an increase of 0.76 mm Hg in BP (3), and increases the risk of developing hypertension by 8.1% (19). On the other hand, decreased Vitamin D levels and increased SBP levels were independent predictors of the presence of multi-organ involvement. The human and animal studies show that the relationship between vitamin D and blood pressure is the result of increased RAAS activation (20-22). Besides, VDD is associated with increased parathormone, which can cause hypertension with both hypertrophy and fibrosis of endothelial smooth muscle cells and increased endothelial calcification (23). Increased parathormone levels result in higher BP (24). Continuous BP load affects the left heart, resulting in left ventricular hypertrophy (25). These direct and indirect effects of vitamin D suggest that it may play a role in myocardial remodeling manifested by cardiac hypertrophy and interstitial fibrosis, which are important indicators of heart failure in hypertension (26).

From VDS to VDSD, CIMT, which is an indicator of subclinical endothelial dysfunction, and LVMI, which is an indicator of hypertrophy were gradually increased. Recent studies show that VDD is an important factor in endothelial dysfunction and cardiac hypertrophy, addition to BP (8, 27, 28). Cardiac hypertrophy is frequently observed in hypertension patients with 25(OH)D deficiency (29). However, endothelial dysfunction is an important change due to hypertensive damage in the central and peripheral arteries, and it precedes cardiac hypertrophy in hypertensive patients and is an important predictor of cardiac hypertrophy (30). This may explain the stronger association between CIMT and Vitamin D levels compared to other TOD indicators in current findings. Besides, the relationship between endothelial dysfunction and cardiac hypertrophy plays an important role in the development or progression of renal damage (31). Renal damage due to hypertension is based on increased urinary albumin excretion as a result of increased intra-glomerular pressure due to decreased kidney functions (32). We found a negative correlation between Vitamin D and microalbuminuria and proteinuria, which is an indicator of early kidney damage. Therefore, vitamin D levels were directly or indirectly related from endothelial dysfunction to heart and kidney damage. This may be due to the relationship between Vitamin D and RAAS activation.

Recent evidence suggests that the Vitamin D plays a role in the inflammatory response (1). We found a negative correlation between Vitamin D and NLR levels in hypertensive patients. In addition, these two parameters were independent predictors of both TOD and multi-organ involvement. Previous hypertensive studies have shown a positive correlation between NLR levels and the presence of TOD (33, 34). Hypertensive experimental studies have shown that vitamin D depletion increases natriuretic peptides and neutrophil activation (5, 35). In spontaneously hypertensive rats, Vitamin D3 deficiency induced neutrophil ROS production, increased micronucleus formation and was associated with induced DNA damage (35). This suggests that Vitamin D participates in the inflammatory response by playing a role in the adaptive and innate immune system in hypertensive organ damage. The negative relationship between vitamin D and CRP and NLR levels supports this hypothesis. Therefore, VDD may be associated with different mechanisms such as RAAS activation and immune-inflammatory response in hypertensive organ involvement, and the coexistence of these relationships may cause more organ involvement. A gradual increase in CRP and NLR levels was detected in patients with multi-organ involvement, but a gradual decrease in vitamin D was detected.

In the current study, we found that the relationship between Vitamin D deficiency and TOD continues regardless of disease duration and anti-hypertensive treatments. Although the effects of traditional risk factors were eliminated in most of the studies, the duration of the disease and the effects of anti-hypertensive drugs were not taken into account. Since the majority of hypertensive patients are in the advanced age group, a decrease in vitamin D levels can be observed (36). The duration of the disease increases with increasing age. For this reason, increasing disease duration may decrease in vitamin D due to aging and increase the severity of TOD due to the rate of atherosclerosis. On

the other hand, considering the effect of Vitamin D on RAAS, the effectiveness of anti-hypertensive treatments may be affected (37, 38). Therefore, in hypertensive patients with VDD, Vitamin D supplementation can reduce the probability of TOD, slow down or prevent the atherosclerotic process, regardless of disease duration or anti-hypertensive drugs. Randomized controlled prospective studies are needed to support this.

Our study has some important limitations. Firstly, 1,25(OH)2D levels of patients could not be measured due to the retrospective study design. Circulating vitamin D levels are transmitted by the VDR signal. Therefore, measured vitamin D levels do not reflect the circulating active form, 1,25(OH)2D. This may be insufficient to fully elucidate the physiological effect of Vitamin D on the development of TOD. Another important limitation is that a marker that directly indicates endothelial damage has not been studied, so it does not provide conclusive evidence between endothelial damage and vitamin D deficiency. In addition, the seasonal variation of vitamin D and the low number of our patients are among our other important limitations.

CONCLUSION

In hypertensive patients, a decrease in vitamin D levels is associated with an increase in TOD indicators. The risk of developing TOD and multi-organ involvement is higher in vitamin D deficiency. Considering the high prevalence of multi-organ involvement in the case of vitamin D deficiency, it is thought that the atherosclerotic process may accelerate. Vitamin D supplements may be beneficial in hypertensive organ damage, regardless of disease duration and anti-hypertensive treatments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Research Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.21).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Jeong HY, Park KM, Lee MJ, Yang DH, Kim SH, Lee SY. Vitamin D and hypertension. Electrolyte Blood Press 2017; 15: 1-11.
2. Mehta V, Agarwal S. Does Vitamin D Deficiency Lead to Hypertension? Cureus 2017; 9: e1038.
3. Ulu SM, Ulasli A, Yaman F, Yaman G, Ozkececi G, Yuksel S. The relationship between vitamin D and PTH levels and cardiovascular risk in the elderly hypertensives. Clin Exp Hypertens 2014; 36: 52-7.
4. Lawler PR, Hiremath P, Cheng S. Cardiac target organ damage in hypertension: insights from epidemiology. Curr Hypertens Rep 2014; 16: 446.
5. Andersen LB, Przybyl L, Haase N, et al. Vitamin D depletion aggravates hypertension and target-organ damage. J Am Heart Assoc 2015; 4: e001417.
6. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients 2020; 12: 575.
7. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. Med Clin North Am 2009; 93: 569-82.
8. Kuloglu O, Gur M, Seker T, et al. Serum 25-hydroxyvitamin D level is associated with arterial stiffness, left ventricle hypertrophy, and inflammation in newly diagnosed hypertension. J Investig Med 2013; 61: 989-94.
9. Yilmaz F, Sozel H. Relationship between 25-hydroxyvitamin D and microalbuminuria in patients with newly diagnosed essential hypertension. Clin Exp Hypertens 2021; 43: 217-22.
10. Lupoli R, Vaccaro A, Ambrosino P, Poggio P, Amato M, Di Minno MN. Impact of Vitamin D deficiency on subclinical carotid atherosclerosis: a pooled analysis of cohort studies. J Clin Endocrinol Metab 2017; 102: 2146-53.
11. Karki A, Vaidhya S, Kunwar D, Kunwar R. Vitamin D Deficiency among Patients Presenting to Outpatient Department of Medicine of a Tertiary Care Centre: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc 2022; 60: 465-8.
12. Meehan M, Penckofer S. The Role of Vitamin D in the Aging Adult. J Aging Gerontol 2014; 2: 60-71.
13. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104.
14. Perrone-Filardi P, Coca A, Galderisi M, et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension. J Hypertens 2017; 35: 1727-41.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-30.
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450-8.
17. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007; 23: 75-80.
18. Liu Y, Shi L, Lin Y, et al. Relationship between serum 25-hydroxyvitamin D and target organ damage in children with essential hypertension. J Hum Hypertens 2022; 36: 604-9.
19. Vimaleswaran KS, Cavadino A, Berry DJ, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. Lancet Diabetes Endocrinol 2014; 2: 719-29.

20. McMullan CJ, Borgi L, Curhan GC, Fisher N, Forman JP. The effect of vitamin D on renin-angiotensin system activation and blood pressure: a randomized control trial. J Hypertens 2017; 35: 822-9.
21. Vaidya A, Williams JS. The relationship between vitamin D and the renin-angiotensin system in the pathophysiology of hypertension, kidney disease, and diabetes. Metabolism 2012; 61: 450-8.
22. Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010; 55: 1283-8.
23. Ke L, Mason RS, Kariuki M, Mpofu E, Brock KE. Vitamin D status and hypertension: a review. Integr Blood Press Control 2015; 8: 13-35.
24. Fisher SB, Perrier ND. Primary hyperparathyroidism and hypertension. Gland Surg 2020; 9: 142-9.
25. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. Prog Cardiovasc Dis 2020; 63: 10-21.
26. Tomek J, Bub G. Hypertension-induced remodelling: on the interactions of cardiac risk factors. J Physiol 2017; 595: 4027-36.
27. Seker T, Gur M, Ucar H, et al. Lower serum 25-hydroxyvitamin D level is associated with impaired myocardial performance and left ventricle hypertrophy in newly diagnosed hypertensive patients. Anatol J Cardiol 2015; 15: 744-50.
28. Carrelli AL, Walker MD, Lowe H, et al. Vitamin D deficiency is associated with subclinical carotid atherosclerosis: the Northern Manhattan study. Stroke 2011; 42: 2240-5.
29. Fallo F, Catena C, Camozzi V, et al. Low serum 25-hydroxyvitamin D levels are associated with left ventricular hypertrophy in essential hypertension. Nutr Metab Cardiovasc Dis 2012; 22: 871-6.
30. Budzyn M, Gryszczynka B, Boruczkowski M, et al. The potential role of circulating endothelial cells and endothelial progenitor cells in the prediction of left ventricular hypertrophy in hypertensive patients. Front Physiol 2019; 10: 1005.
31. Poulikakos D, Ross L, Recio-Mayoral A, et al. Left ventricular hypertrophy and endothelial dysfunction in chronic kidney disease. Eur Heart J Cardiovasc Imaging 2014; 15: 56-61.
32. Mule G, Castiglia A, Cusumano C, et al. Subclinical kidney damage in hypertensive patients: A renal window opened on the cardiovascular system. focus on microalbuminuria. Adv Exp Med Biol 2017; 956: 279-306.
33. Sevencan NO, Ozkan AE. Associations between neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albuminuria and uric acid and the estimated glomerular filtration rate in hypertensive patients with chronic kidney disease stages 1-3. Arch Med Sci 2019; 15: 1232-9.
34. Wang H, Hu Y, Geng Y, et al. The relationship between neutrophil to lymphocyte ratio and artery stiffness in subtypes of hypertension. J Clin Hypertens (Greenwich) 2017; 19: 780-5.
35. Machado Cda S, Venancio VP, Aissa AF, et al. Vitamin D3 deficiency increases DNA damage and the oxidative burst of neutrophils in a hypertensive rat model. Mutat Res Genet Toxicol Environ Mutagen 2016; 798-799: 19-26.
36. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North Am 2013; 42: 319-32.
37. Legarth C, Grimm D, Wehland M, Bauer J, Kruger M. The impact of Vitamin D in the treatment of essential hypertension. Int J Mol Sci 2018; 19: 455.
38. Sheikh V, Mozaianimonfared A, Gharakhani M, Poorolajal J, Ph D. Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial. J Clin Hypertens (Greenwich) 2020; 22: 1867-73.