The Investigation of the Calcium Metabolism Changes in Rheumatic Mitral Valve Patients

Aziz İnan Çelik[1](İD), Reşit Coşkun[2](İD), Muhammet Buğra Karaaslan[3](İD), Tahir Bezgin[1](İD), Süleyman Karakoyun[4](İD), Metin Çağdaş[1](İD)

[1] Clinic of Cardiology, Heart Center, Gebze Fatih State Hospital, Kocaeli, Turkey
[2] Department of Cardiology, Erzincan Binali Yıldırım University Faculty of Medicine, Erzincan, Turkey
[3] Clinic of Cardiology, Osmancık State Hospital, Çorum, Turkey
[4] Clinic of Cardiology, Akademi Hospital, Kocaeli, Turkey

ABSTRACT

Introduction: Rheumatic mitral valve disease (RMVD) is associated with autoimmune heart valve injury. Parathyroid hormone (PTH) and vitamin D are two essential molecules that have effects on the immune system. In this study, we aimed to evaluate the relationship between PTH and vitamin D in patients with RMVD.

Patients and Methods: We investigated 81 patients with RMVD and 75 healthy subjects. According to Wilkins score, baseline clinical, laboratory, and echocardiographic parameters were recorded, and all RMVD patients were analyzed. Multivariate logistic regression analysis was performed between the groups.

Results: Vitamin D levels were significantly low in the RMVD group. Patients were stratified according to Wilkins score [Wilkins score <7 (n= 50) vs. Wilkins score ≥7 (n= 31)]. Age, BMI, and PTH were significantly higher, and mitral valve area was significantly lower in Wilkins score ≥7 patients. In multivariate analysis, age (OR= 1.052; 95% CI 1.005-1.100, p= 0.028) and PTH (OR= 1.017; 95% CI 1.000-1.033, p= 0.047) were found to be independent predictors of high Wilkins score.

Conclusion: This study showed that vitamin D levels were low in patients with RMVD. According to the Wilkins score, PTH levels were significantly high in patients with a high Wilkins score. Changes in PTH and vitamin D levels may trigger inflammation and be responsible for valve damage.

Key Words: Mitral valve; parathyroid hormone; vitamin D; inflammation

Romatizmal Mitral Kapak Hastalarında Kalsiyum Metabolizması Değişikliklerinin Araştırılması

ÖZET

Giriş: Romatizmal mitral kapak hastalığı (RMKH), otoimmün kalp kapak hasarı ile ilişkilidir. Paratiroid hormon (PTH) ve D vitamini, bağışıklık sistemi üzerinde etkileri olan iki temel moleküldür. Bu çalışmada PTH ve D vitamininin RMKH'lı hastalar arasındaki ilişkisini değerlendirmeyi amaçladık.

Hastalar ve Yöntem: Çalışmaya RMKH›lı 81 hasta ve 75 kontrol grubu dahil edildi. Wilkins skoruna göre başlangıç klinik, laboratuar ve ekokardiyografik parametreler kaydedildi ve tüm RMKH olan hastalar analiz edildi. Gruplar arasında çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: RMKH grubunda D vitamini seviyeleri anlamlı derecede düşüktü. Hastalar Wilkins skoruna göre sınıflandırıldı [Wilkins skoru <7 (n=50) ve Wilkins skoru ≥7 (n=31)]. Wilkins skoru ≥7 olan hastalarda yaş, vücut kitle indeksi ve PTH anlamlı olarak daha yüksekti ve mitral kapak alanı anlamlı olarak daha düşüktü. Çok değişkenli analizde, yaş (OR= 1.052; %95 CI 1.005-1.100, p= 0.028) ve PTH (OR= 1.017; %95 CI 1.000-1.033, p= 0.047), yüksek Wilkins skorunun bağımsız prediktörleri olarak bulundu.

Sonuç: Bu çalışma, RMKH'lı hastalarda D vitamini düzeylerinin düşük olduğunu göstermiştir. Wilkins skoru yüksek olan hastalarda ise PTH düzeyleri anlamlı olarak yüksekti. PTH ve D vitamini seviyelerindeki değişiklikler inflamasyonu tetikleyebilir ve kapak hasarından sorumlu olabilir.

Anahtar Kelimeler: Mitral kapak; paratiroid hormonu; vitamin D; inflamasyon

INTRODUCTION

Rheumatic mitral valve disease (RMVD) is the most common cause of mitral valve stenosis worldwide, is more common in developing countries, and progresses faster. It is an immune response that occurs with cross-reactivity between streptococcal antigen and valve tissue[(1)]. Patients who have recurrent acute rheumatic fever carditis are more likely to de-

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Correspondence

Aziz İnan Çelik

E-mail: azizinanmd@hotmail.com
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velop RMVD. Mitral valve can be affected in 50% of patients and results in mitral stenosis, mitral insufficiency, or both[2,3]. Inflammation, fibrosis, and calcification are the essential factors in the progression of mitral stenosis due to autoimmune heart valve damage after streptococcal infection. Wilkins calcification scoring is a widely used scoring system to determine the disease's severity in rheumatic mitral stenosis[4].

Parathyroid hormone (PTH) and vitamin D are the primary regulators of calcium balance and bone mineral turnover. Increased PTH (primary or secondary) levels bear a high risk of cardiovascular mortality and cause cardiovascular diseases such as coronary microvascular dysfunction, valvular calcification, increased vascular stiffness, endothelial dysfunction, and hypertension[5,6]. On the other hand, vitamin D, another vital hormone of calcium metabolism, is involved in suppressing the inflammatory process[7]. Studies conducted in previous years have shown that low levels of vitamin D are associated with RMVD[8]. On the other hand, high levels of vitamin D have been shown to play a role in tissue calcification[9-11]. Therefore, abnormally high or abnormally low vitamin D can cause heart valve diseases with different mechanisms.

This study aimed to examine the relationship between PTH, vitamin D, serum calcium, and serum phosphate levels in patients with RMVD.

PATIENTS and METHODS

Eighty-one patients with RMVD and 75 healthy age and gender-matched control subjects were enrolled after the exclusion criteria. Exclusion criteria were defined as follows; age <18, pregnancy, alcohol consumption, chronic renal failure (Cockcroft-Gault GFR< 60 mL/min/1.73 m^2) (n= 5), chronic hepatic failure (ALT and AST levels higher than 3-folds of normal levels), pancreatitis, celiac disease, malignancy (n= 1), tumor lysis syndrome, primary hypoparathyroidism, and hyperparathyroidism, hypothyroidism (n= 7), hyperthyroidism (n= 3), acute or chronic inflammatory, and autoimmune diseases, metabolic bone diseases, heart valve surgery history, bariatric surgery history, medication use that may affect PTH levels (n= 9). The study protocol was reviewed and approved by the Local Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants. The patients' age, gender, smoking status, body mass index (BMI), systolic blood pressure, heart rate, laboratory and echocardiographic parameters were recorded in detail.

Transthoracic echocardiographic examinations were performed using Philips Epiq 7G Ultrasound System (Philips, The Netherlands) (S8-3, 3-8 MHz probes). Left ventricular ejection fraction (EF), systolic pulmonary arterial pressure (sPAP), planimetric mitral valve area, mitral valve gradients, mitral valve pressure half-time, mitral insufficiency (MR), and aortic insufficiency (AR) were measured with 2D-transthoracic echocardiography. Wilkins scores (leaflet mobility, valvular calcification, valvular thickening, and subvalvular thickening) were calculated in RMVD. All valvular measurements were performed and classified according to the 2020 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease[12].

Venous blood samples were obtained to dry tubes from all patients on admission. Fasting blood glucose, creatinine, sodium, potassium, albumin, calcium, corrected calcium [measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin) (g/dL)] and phosphorus were measured using a Roche Cobas C501 autoanalyzer system (Roche Diagnostics, Indianapolis, IN, USA). A standard enzymatic method with an AU6B0 autoanalyzer (Beckman Coulter, Brea, CA) was used for the measurement of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. A standard nephelometry method was used to measure C-reactive protein levels (CRP) (Cobas c311; Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.1 mg/L. Vitamin D concentration was measured with automatic direct electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics), and the electrochemiluminescence microparticle immunoassay was used to measure PTH levels with a Cobase 601 kit (Roche Diagnostics).

Data were analyzed using SPSS 22.0 version (SPSS Inc, Chicago, Illinois). The continuous variables with a normal distribution of mean ± SD and t-test are used in group comparison. In contrast, those without a normal distribution are presented as median (interquartile range). Categorical variables are shown as numbers and percent (%). Categorical data were compared using the Chi-square or Fisher's exact test. Group comparison was performed with the Mann-Whitney U test. Correlations between variables were assessed by the Pearson correlation test for continuous variables and the Spearman test for non-continuous variables. Statistical significance was defined as a p-value <0.05. Multivariate logistic regression analysis was used to determine the independent predictors of the high Wilkins score.

RESULTS

A total of 156 patients (81 RMVD group and 75 control group) were enrolled. Fifty-five patients (67.9%) in the RMVD group and 45 patients (60%) in the control group were female. Baseline characteristics and laboratory parameters of the study population are demonstrated in Table 1. All baseline characteristics and laboratory parameters were similar between the

Table 1. The baseline clinical and laboratory characteristics of the RMVD patients and control group

	RMVD (n= 81)	Controls (n= 75)	Total (n= 156)	p
Age	42 (35-50)	43 (37-49)	43 (36.5-50)	0.907
Gender (Female), n (%)	55 (67.9)	45 (60)	100 (64.1)	0.321
Smoking, n (%)	15 (18.5)	21 (28)	36 (23.1)	0.188
BMI (kg/m^2)	26 ± 4	26.5 ± 4.7	26.2 ± 4.4	0.635
Systolic blood pressure, mmHg	110.2 ± 9.5	108.8 ± 9.6	109.5 ± 9.5	0.434
Heart rate, bpm	76 ± 13	74 ± 15	75 ± 14	0.303
Ejection fraction, %	61.4 ± 3.5	62.1 ± 2.6	61.7 ± 3.1	0.506
Fasting blood glucose, mg/dL	79 (59-89)	77 (63-90)	78 (61-89)	0.529
Creatinine, mg/dL	0.91 (0.77-1.09)	0.96 (0.76-1.14)	0.93 (0.77-1.10)	0.552
GFR, (mL/min/1.73 m^2)	110 ± 6	111 ± 7	111 ± 7	0.372
Sodium, mEq/L	138 ± 3	138 ± 4	138 ± 3	0.703
Potassium, mEq/L	3.9 ± 0.2	3.9 ± 0.3	3.8 ± 0.3	0.576
Albumin, g/dL	4.3 ± 0.3	4.5 ± 0.4	4.4 ± 0.3	0.003
Calcium, mg/dL	9.5 ± 0.5	9.5 ± 0.4	9.5 ± 0.5	0.780
Corrected calcium, mg/dL	9.2 ± 0.5	9.1 ± 0.4	9.2 ± 0.5	0.076
Phosphorus, mg/dL	3.7 (3.2-4.3)	3.6 (3-4.2)	3.6 (3.1-4.1)	0.724
Vitamin D, ng/mL	11.3 (8.7-16.3)	17.7 (11.8-21)	14.3 (9.9-20.5)	<0.001
Parathyroid hormone, pg/mL	63.4 (48.6-81)	61 (47-88)	60.7 (47.1-81)	0.582
CRP, mg/dL	0.6 (0.2-1.6)	0.3 (0.1-1.1)	0.4 (0.1-1.5)	0.147
Total cholesterol, mg/dL	178 (156-201)	165 (145-196)	170 (147.5-198.5)	0.132
LDL-C, mg/dL	106 (86-129)	98 (78-119)	101.5 (80-125)	0.085
HDL-C, mg/dL	40 (37-43)	44 (39-51)	42 (38-46.5)	<0.001
Triglyceride, mg/dL	166 (123-211)	143 (109-181)	154 (117-191.5)	0.095

RMVD: Rheumatic mitral valve disease, BMI: Body mass index, GFR: Glomerular filtration rate, CRP: C-Reactive protein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol.

two groups except albumin, vitamin D, and HDL-C. albumin, vitamin D and HDL-C levels were significantly low in RMVD group [4.3 ± 0.3 vs. 4.5 ± 0.4, p= 0.003; 11.3 (8.7-16.3) vs. 17.7 (11.8-21), p< 0.001; 40 (37-43) vs. 44 (39-51), p< 0.001, respectively]. However, there were no differences in PTH, calcium, corrected calcium, and phosphorus levels.

Patients were stratified according to Wilkins score [Wilkins score <7 (n= 50) vs. Wilkins score ≥7 (n= 31)]. Age, BMI, PTH, mean pressure gradient, pressure half-time of the mitral valve, and sPAP were significantly higher, and mitral valve area was significantly lower in Wilkins score ≥7 patients [40.5 (30-47) vs. 48 (40-56), p= 0.015; 25.2 ± 3.7 vs. 27.2 ± 4.2, p= 0.026; 56.1 (39.5-78.6) vs. 79 (57-91), p= 0.008; 2.5 (1.8-3.5) vs. 5.7 (3-7.2), p< 0.001; 88.6 ± 13.3 vs. 136.9 ± 43.7, p< 0.001; 18.5 ± 2.8 vs. 28.8 ± 12.1, p< 0.001; 4 (3-4.5) vs. 2.1 (1.4-2.9), p< 0.001, respectively] (Table 2). There was no symptomatic severe MR and AR (stage D) in either group. Progressive MR (stage B) and asymptomatic severe MR (stage C) were significantly higher in patients with a Wilkins score of ≥7 for MR (p= 0.029). Similarly, stage A and stage B AR were significantly higher in patients with a Wilkins score of ≥7 (p= 0.002).

The correlation between age, vitamin D, PTH levels and mitral valve area, mean pressure gradient of the mitral valve, and Wilkins score was investigated. There was a negative correlation between advanced age and mitral valve area; a positive correlation between mean pressure gradient and Wilkins score found (-0.269, p= 0.015; 0.235, p= 0.035; 0.291, p= 0.008). There is a significant correlation between vitamin D and the mitral valve area (0.223, p= 0.045). A negative correlation between PTH and mitral valve area, a positive correlation between mean pressure gradient and Wilkins score were found (-0.403, p< 0.001; 0.291, p= 0.008; 0.327, p= 0.003) (Table 3) (Figure 1-2).

Table 2. Clinical, laboratory and echocardiographic parameters according to Wilkins score

		Wilkins score< 7, n= 50	Wilkins score≥ 7, n= 31	Total, n= 81	p
Age		40.5 (30-47)	48 (40-56)	42 (35-50)	0.015
Gender (Female), n (%)		33 (66)	22 (71)	55 (67.9)	0.624
Smoking, n (%)		10 (20)	5 (16.1)	15 (18.5)	0.442
BMI (kg/m^2)		25.2 ± 3.7	27.2 ± 4.2	26 ± 4	0.026
Systolic blood pressure, mmHg		110.1 ± 9.3	110.3 ± 9.8	110.2 ± 9.5	0.838
Heart rate, bpm		77.5 ± 12.2	75.1 ± 14.9	76.6 ± 13.3	0.466
Ejection fraction, %		61.8 ± 3.9	60.8 ± 2.8	61.4 ± 3.5	0.109
Fasting blood glucose, mg/dL		78 (60-89)	81 (58-88)	79 (59-89)	0.977
Creatinine, mg/dL		0.91 (0.77-1.09)	0.91 (0.77-1.08)	0.91 (0.77-1.09)	0.627
GFR, (mL/min/1.73 m^2)		110 ± 7	110 ± 6	110 ± 6	0.387
Sodium, mEq/L		139 ± 4	137 ± 3	138 ± 3	0.354
Potassium, mEq/L		3.8 ± 0.3	4 ± 0.2	3.9 ± 0.2	0.346
Albumin, g/dL		4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	0.406
Calcium, mg/dL		9.5 ± 0.5	9.4 ± 0.6	9.5 ± 0.5	0.202
Corrected calcium, mg/dL		9.3 ± 0.4	9.1 ± 0.6	9.2 ± 0.5	0.391
Phosphorus, mg/dL		3.6 (3.2-4)	3.4 (3.2-4)	3.7 (3.2-4.3)	0.566
Vitamin D, ng/mL		11.6 (8-16.9)	11 (8.7-15.6)	11.3 (8.7-16.3)	0.934
PTH, pg/mL		56.1 (39.5-78.6)	79 (57-91)	61 (47-88)	0.008
CRP, mg/dL		0.5 (0.2-1.6)	0.6 (0.1-1.7)	0.6 (0.2-1.6)	0.868
Total cholesterol, mg/dL		176 (156-201)	178 (144-202)	178 (156-201)	0.726
LDL-C, mg/dL		106 (87-128)	119 (73-133)	106 (86-129)	0.853
HDL-C, mg/dL		40 (38-43)	39 (35-44)	40 (37-43)	0.365
Triglyceride, mg/dL		160.5 (123-215)	168 (111-187)	166 (123-211)	0.903
Mitral valve area, cm^2		4 (3-4.5)	2.1 (1.4-2.9)	3.2 (2.4-4.2)	<0.001
Mean pressure gradient, mmHg		2.5 (1.8-3.5)	5.7 (3-7.2)	3 (2-5)	<0.001
Pressure half-time, ms		88.6 ± 13.3	136.9 ± 43.7	107.1 ± 37.2	<0.001
sPAP, mmHg		18.5 ± 2.8	28.8 ± 12.1	22.5 ± 9.2	<0.001
Mitral regurgitation, n (%)	None	27 (54)	10 (32.3)	37 (45.7)	0.029
	A	18 (36)	12 (38.7)	30 (37)	
	B	5 (10)	5 (16.1)	10 (12.3)	
	C	0 (0)	4 (12.9)	4 (4.9)	
	D	0 (0)	0 (0)	0 (0)	
Aortic regurgitation, n (%)	None	32 (64)	9 (29)	41 (50.6)	0.002
	A	18 (36)	19 (61.3)	37 (45.7)	
	B	0 (0)	3 (9.7)	3 (3.7)	
	C	0 (0)	0 (0)	0 (0)	
	D	0 (0)	0 (0)	0 (0)	

BMI: Body mass index, GFR: Glomerular filtration rate, PTH: Parathyroid hormone, CRP: C-Reactive protein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, sPAP: Systolic pulmonary arterial pressure.

Table 3. Correlation between age, vitamin D and PTH with high Wilkins score

		Mitral valve area	Mean pressure gradient	Wilkins score
Age	Correlation Coefficient	-0.269	0.235	0.291
	p value	0.015	0.035	0.008
Vitamin D	Correlation Coefficient	0.223	-0.041	-0.020
	p value	0.045	0.719	0.860
PTH	Correlation Coefficient	-0.403	0.291	0.327
	p value	<0.001	0.008	0.003

PTH: Parathyroid hormone.

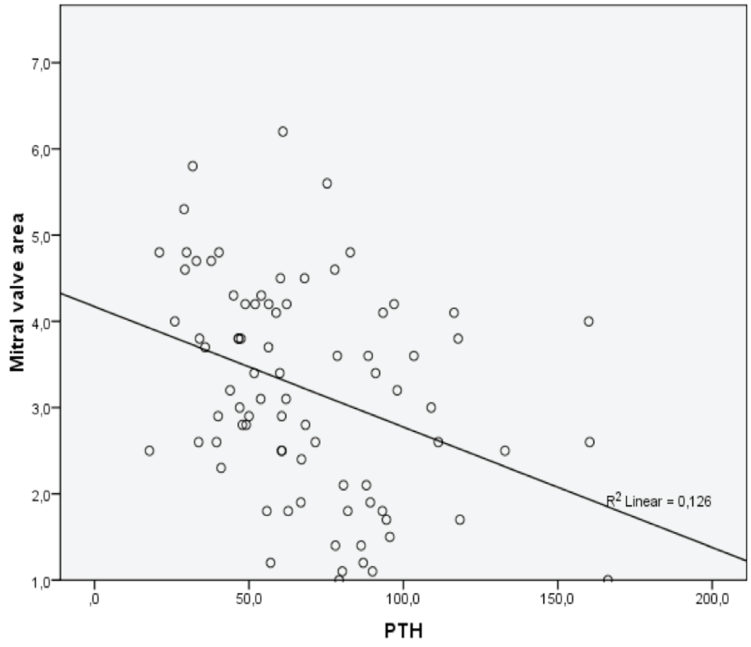

Figure 1. Negative correlation between PTH and mitral valve area.
PTH: Parathyroid hormone.

Multivariate logistic regression analysis was performed using parameters (age, BMI, and PTH) that differed between the groups to determine the independent predictors of the high Wilkins score. In multivariate analysis, age (OR= 1.052; 95% CI 1.005-1.100, p= 0.028) and PTH (OR= 1.017; 95% CI 1.000-1.033, p= 0.047) were found to be independent predictors of high Wilkins score.

DISCUSSION

To the best of our knowledge, this is the first study to assess the serum vitamin D and PTH in RMVD. We aimed to evaluate the changes in calcium metabolism at the beginning of the disease. The present study found that vitamin D levels were significantly lower in RMVD than in control subjects. However, there was no significant difference in PTH between the two groups. When patients were grouped according to Wilkins score, the opposite results were obtained. PTH was significantly higher in the high Wilkins score group (Wilkins score≥ 7). Yet, this difference was not significant for vitamin D. When the literature was reviewed, very few studies examined calcium metabolism changes in patients with RMVD. In addition, chronic inflammation, recurrent carditis attacks, low socioeconomic status, and increased PTH levels were associated with a high Wilkins score.

Molecular similarities between streptococcal antigens such as M protein and cardiac tissue proteins activate the CD4 + T cells and cause valve damage[13]. RMVD is an autoimmune valvular disorder that causes progressive and devastating consequences. Disequilibrium between pro- and anti-inflammatory

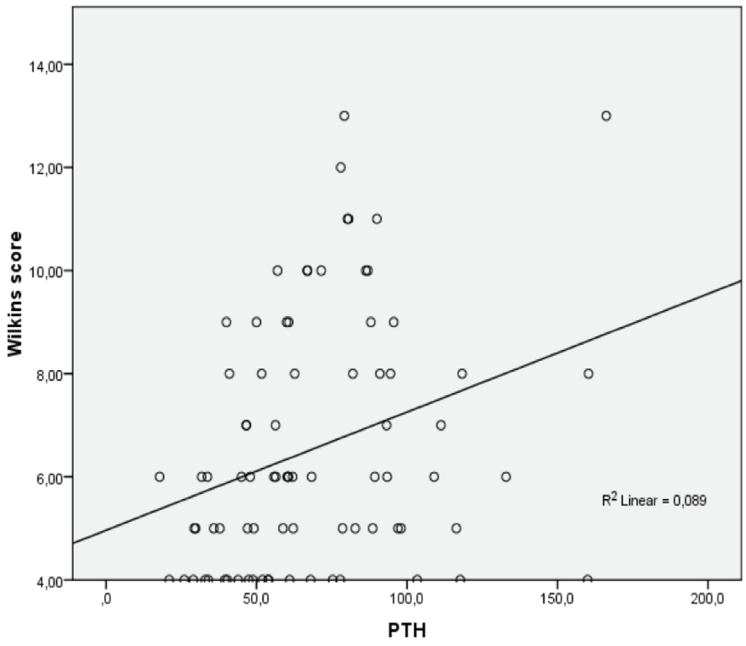

Figure 2. Positive correlation between PTH and Wilkins score.
PTH: Parathyroid hormone.

cells induces the target organ damage in all autoimmune diseases[14]. These CD4 + T cells transform into Th1 helper cells, causing tissue damage by secreting cytokines such as tumor necrosis factor-alpha (TNF-a), interferon, interleukin (IL)-17, IL-22. TNF has also been shown to increase calcification by promoting differentiation of valve interstitial cells to osteoblasts[15-18].

Vitamin D has several effects on T cells that can modulate the immune response[19]. This effect occurs through vitamin D receptors (VDR), identified on CD4 + T cells[20]. VDRs are in the nuclear steroid/thyroid hormone receptor family and are located in the bone marrow and thymus[21]. Besides CD4 + T cells, VDRs have also been identified in mononuclear cells, dendritic cells, and activated B lymphocytes. Vitamin D inhibits the proliferation of effector CD4 + T cells while contributing to the development of anti-inflammatory T cells[22, 23]. Vitamin D also inhibits the production of inflammatory cytokines such as TNF-a produced by Th1 helper T cells, ¡ interferon, and IL-17 produced by Th17 helper T cells[24,25]. Th1 functions are inhibited by IL-4 and IL-10, which were produced by another T cell, Th2. Overberg et al. have shown that vitamin D increases IL-4 levels in in-vivo conditions[26].

On the other hand, vitamin D inhibits B lymphocyte proliferation, conversion to plasma cells, and antibody secretion. In vitamin D deficiency, this inflammatory balance is disrupted in favor of proinflammation and contributes to valve damage in RMVD. Clinical studies support this molecular mechanism. In the study conducted by Yusuf et al., vitamin D levels were significantly lower in patients with damaged and severe calcified RMVD than in patients with less damaged and non-calcified RMVD[27]. In the same study, vitamin D levels correlated with the Wilkins score and Wilkins calcification score. In another study conducted by Yavuz et al., the control and patient groups with RMVD were compared. Patients with RMVD had a significantly lower vitamin D level than the control group and correlated with Wilkins score[8]. As in the literature, in our study, the vitamin D levels of patients with RMVD were lower than in the control group. There is also a significant correlation between vitamin D and the mitral valve area. According to Wilkins score, vitamin D level was lower in patients with high Wilkins scores, but this finding was not statistically significant.

Parathyroid hormone (PTH) is the primary regulator of calcium balance in physiological and pathological conditions and plays an essential role in bone hemostasis. PTH may play a role beyond the one in mineral and bone metabolism in the pathophysiology of vascular and cardiovascular diseases. Clinically, patients with primary hyperparathyroidism have a higher risk of cardiovascular mortality and have a broad spectrum of cardiovascular diseases such as coronary microvascular dysfunction, subclinical aortic valve calcification, increased aortic stiffness, endothelial dysfunction, and hypertension[28]. Besides, secondary hyperparathyroidism, a significant complication in patients with chronic kidney disease, causes abnormal bone disorders, non-skeletal calcification such as vascular and

valvular calcification, and increased cardiovascular mortality. Many studies have shown that high serum PTH levels have a proinflammatory effect. In a study by Cheng et al., a relation was found between high PTH levels and various inflammatory markers (C-reactive protein, the modified Glasgow Prognostic Score, red cell distribution width, and the platelet-to-lymphocyte ratio)[29].

There is a strong relationship between vitamin D and PTH. A decrease in vitamin D levels leads to a reduction in calcium absorption from the intestine, and the organism responds by increasing the secretion of PTH. As a result, there is an inverse correlation between PTH and vitamin D. In a study by Linhartova et al., high PTH and low vitamin D levels are associated with calcific aortic stenosis in coronary artery patients[10]. In another study, Eren et al. compared 56 chronic heart valve patients (AR and MR) with the control group. Compared to the control group, vitamin D levels are significantly low, and PTH is higher in patients with heart valve disease[30]. Yusuf et al. demonstrated the relationship between the severity of the disease and the PTH level in patients with RMVD[27]. In our study, RMVD had higher PTH levels than the control group; however, there were no significant differences between the two groups. According to the Wilkins score, PTH was significantly higher in patients with a high Wilkins score. Apart from the Wilkins score, there is a positive correlation between PTH and the mitral valve area and a negative correlation between PTH and the mean pressure gradient.

The present study has several limitations. First, the number of patients was relatively low. Second, this study involves only non-stenotic rheumatic mitral valves. However, stenotic rheumatic mitral valves may affect calcium metabolism more significantly. Third, this study did not contain the follow-up data of the patients. Finally, it has a cross-sectional design.

CONCLUSION

In conclusion, in this study, we investigated the inflammatory response caused by the change in PTH and vitamin D levels and the resulting contribution to rheumatic change in the mitral valve. Vitamin D level was lower in patients with RMVD compared to the control group. According to the Wilkins score, the PTH level was significantly higher in patients with a high score. Future studies with larger populations are warranted to clearly identify the relationship between RMVD and vitamin D and PTH.

Ethics Committee Approval: The study was approved by the Health Sciences University Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee (Date: 25.02.2021, Decision No: 2020/135).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - AİÇ; Analysis/Interpretation - SK; Data Collection - AİÇ; Writing - TB; Critical Revision - MÇ; Final Approval - RC; Statistical Analysis - MÇ; Overall Responsibility - RC.

Conflict of Interest: The authors declared that there was no conflict of interest during the preparation and publication of this article.

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