ORIGINAL ARTICLE

Impact of 25(OH)D_3 on spontaneous reperfusion and SYNTAX score in patients with ST-elevation myocardial infarction

ST yükselmeli miyokart enfarktüsünde 25(OH)D_3 seviyesinin spontan reperfüzyon ve SYNTAX skoru üzerine etkisi

Oğuz Akkuş, M.D., Mustafa Topuz, M.D., Fahrettin Öz, M.D., Hazar Harbalıoğlu, M.D., Hasan Koca, M.D., Mehmet Kaplan, M.D., Ömer Şen, M.D., Atilla Bulut, M.D., Mustafa Gür, M.D.

Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey

ABSTRACT

Objective: The aim of this study was to evaluate the potential relationship between 25-hydroxyvitamin D_3 (25[OH]D_3), the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, and spontaneous reperfusion (SR) in patients with ST-elevation myocardial infarction (STEMI).

Methods: A total of 148 consecutive patients with acute STEMI who underwent primary percutaneous coronary intervention were retrospectively enrolled in the study.

Results: In all, 36 patients with a TIMI 3 flow score (spontaneous reperfusion [SR]) before coronary intervention constituted Group 1, and 112 patients with a TIMI flow score of 0-2 served as Group 2. The SYNTAX score and the in-hospital major adverse cardiovascular event (MACE) rate were significantly higher in Group 2 (p<0.001, p=0.012, respectively). The mean 25(OH)D_3 level was significantly higher in Group 1 (p=0.003). Age, Killip class, left ventricular ejection fraction, and N-terminal pro-B-type natriuretic peptide were correlated with the SYNTAX score, and 25(OH)D_3, troponin-I, C-reactive protein, and creatinine were weakly correlated with the SYNTAX score. Multilogistic regression analysis indicated that the SYNTAX score (p<0.001), Rentrop collateral (p=0.049), and troponin-I (p=0.004) were significantly effective at predicting SR, and 25(OH)D_3 (p=0.079) and high-density lipoprotein (p=0.055) were borderline effective.

Conclusion: A lower level of 25(OH)D_3 may be associated with the absence of SR, increased disease severity, and in-hospital MACE rates in patients with STEMI.

ÖZET

Amaç: Bu çalışmada, ST yükselmeli miyokart enfarktüsünde (STEMI) spontan reperfüzyon (SR), 25-hidroksivitamin D_3 (25[OH]D_3) ve SYNTAX skoru arasındaki ilişkileri incelemeyi planladık.

Yöntemler: Geriye dönük olarak STEMI tanısı ile perkütan koroner girişim (PKG) uygulanan toplam 148 hasta çalışmaya alındı.

Bulgular: Perkütan koroner girişim öncesi TIMI 3 akıma sahip (spontan reperfüzyon) toplam 36 hasta grup 1, TIMI 0-2 akıma sahip toplam 112 hasta grup 2 olarak ayrıldı. SYNTAX skoru ve majör istenmeyen kardiyak olay (MACE) sıklığı grup 2'de daha yüksek bulundu (sırasıyla, p=<0.001, p=0.012). Ortalama 25(OH)D_3 seviyesi grup 1 hastalarda belirgin olarak yüksek saptandı (p=0.003). Yaş, Killip sınıfı, sol ventrikül ejeksiyon fraksiyonu ve serum N-terminal pro-B-tip natriüretik peptit SYNTAX skoru ve 25(OH)D_3 ile korelasyon gösterirken, troponin-I, C-reaktif protein ve kreatinin sadece SYNTAX skoru ile zayıf korelasyon gösterdi. Spontan reperfüzyon için yapılan multilojistik regresyon analizinde, SYNTAX skoru (p<0.001), Rentrop kollateral varlığı (p=0.049) ve troponin-I seviyesi (p=0.004) belirgin, 25(OH)D_3 (p=0.079) ve düşük yoğunluklu lipoprotein (p=0.055) seviyeleri ise istatistiksel olarak sınırda anlamlı bulundu.

Sonuç: ST yükselmeli miyokart enfarktüsü hastalarında düşük 25(OH)D_3 seviyeleri spontan reperfüzyonun olmayışı, artmış SYNTAX skoru ve hastane içi mortalite ile ilişkili olabilir.

Acute coronary syndromes, especially ST-elevation myocardial infarction (STEMI), are a leading health problem and cause of sudden death. [1] Early revascularization and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow are the primary objectives for patient survival.[1] A TIMI 3 flow in the infarct-related artery (IRA) before primary percutaneous coronary intervention (pPCI) is defined as spontaneous reperfusion (SR), and is associated with better outcomes during perioperative

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Correspondence: Dr. Mustafa Topuz. Adana Numune Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Adana, Turkey.
Tel: +90 322 - 355 01 50 e-mail: mtpuz@hotmail.com

angiography and short-term monitoring.[2,3]

Vitamin D is a fat-soluble steroid that regulates gene expression. The inactive form of vitamin D (vitamin D_3) requires enzymatic conversion via QUA-hydroxylation, and is converted to the essential form of 25-hydroxyvitamin D [25(OH)D_3] in the liver and 1,25(OH)2 vitamin D_3 in the kidney.[4] The prominent form of vitamin D that circulates in the blood is 25(OH)D_3. A deficiency of 25(OH)D_3 plays a crucial role in chronic inflammatory diseases.[5] The anti-inflammatory effects of 25(OH)D_3 are well known; inflammation is more apparent with lower levels of 25(OH)D_3.[6] In addition, a lower level of 25(OH)D_3 is associated with major cardiovascular risk factors,[7] and is a predictor of endothelial dysfunction,[8] coronary artery disease, and mortality in acute coronary syndromes.[9,10] Low 25(OH)D_3 is an independent risk factor for the severity of stable coronary artery disease as calculated using the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score.[11] To our knowledge, there has been no previous study examining the association between 25(OH)D_3 level in SR and SYNTAX score in the acute phase of STEMI. Since a low level of 25(OH)D_3 is associated with increased cardiac events, the goal of this research was to evaluate potential relationships between 25(OH)D_3, the SYNTAX score, and SR in patients with STEMI.

METHODS

Study population

A total of 148 consecutive patients diagnosed with acute ST-elevation myocardial infarction (STEMI) who underwent pPCI were retrospectively enrolled in the present study. Patients whose 25(OH)D_3 values were available in our database between November 2015 and March 2016 were included. None of the patients were taking a steroid, calcium, or vitamin D supplement. Patients with chronic liver and kidney diseases were excluded from the study. Our study was approved by the local ethics committee (date: 10/06/2016, number:54)

Echocardiographic techniques and calculations were performed according to professional recommendations, and the left ventricular ejection fraction (LVEF) was calculated using modified Simpson's rule technique.[12]

The patient's hemodynamic status was recorded according to the Killip classification.[13]

Abbreviations:

25(OH)D_3	*25-hydroxyvitamin D3*
CGMP	*Cyclic guanosine monophosphate*
CI	*Confidence interval*
CRP	*C-reactive protein*
HDL	*High-density lipoprotein*
IRA	*Infarct-related artery*
LVEF	*Left ventricular ejection fraction*
MACE	*Major adverse cardiovascular event*
NT-proBNP	*N-terminal prohormone of brain natriuretic peptide*
pPCI	*Primary percutaneous coronary intervention*
SR	*Spontaneous reperfusion*
STEMI	*ST-elevation myocardial infarction*
SYNTAX	*Synergy between PCI with Taxus and Cardiac Surgery*
TIMI	*Thrombolysis in Myocardial Infarction*

Blood samples

Fasting venous blood samples were obtained from all patients to determine routine laboratory parameters. Serum glucose, creatinine, and lipid profiles were analyzed for each patient. The serum vitamin D level was measured using a direct competitive chemiluminescent immunoassay (Elecsys; Roche Diagnostics, Basel, Switzerland).

Primary percutaneous coronary intervention and SYNTAX score

A standard coronary angiography and pPCI was performed using a Siemens Medical Systems angiography system (Siemens Healthineers, GmbH, Erlangen, Germany) or a Toshiba Infinix CC-i monoplan cardiac angiography system (Toshiba, Inc., Tokyo, Japan) using a 6- or 7-F diagnostic-guiding catheter and the standard Judkins technique via a femoral (left or right) or radial approach by an experienced interventional cardiologist. The SYNTAX score was calculated using angiographic analysis of coronary lesions with a diameter stenosis of ≥50% in vessels with a minimum diameter of ≥1.5 mm defined by a computer program that examined total occlusion, bifurcation, trifurcation, distal vessel bed, thrombus formation, and other elements.[14] The SYNTAX score was calculated before wiring or pre-dilatation of the IRA. A coronary categorization was created according to the Rentrop classification: Rentrop 0: No existing collaterals, 1: existing collaterals that do not reach the epicardial artery, 2: partial filling of the epicardial artery, 3: complete filling of the main epicardial vessel.[15] The TIMI flow grade was also assessed as previously described.[16]

Statistical analysis

The statistical analysis was performed using SPSS

for Windows Version 15.0 (SPSS Inc., Chicago, IL, USA). The study variables were analyzed using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine normal distribution and were expressed as mean±SD or median and interquartile range (range from the 25th to the 75th percentile). The Mann-Whitney U test was used for the comparison of 2 groups with a non-normal distribution of variables and a chi-square test was used for the comparison of qualitative data. Fisher's exact test was performed when the categories were less than the expected value of 5. Comparisons between the 2 groups were carried out using an independent samples t-test. Degrees of association between variables were evaluated using the Pearson's product-moment or Spearman's rank correlation test, as applicable. Multilogistic regression analysis was used to determine independent factors for SR. All of the significant parameters (p<0.25) in the first model were added to the second model. A 2-tailed p<0.05 was considered statistically significant.

RESULTS

A total of 148 consecutive patients (102 male, 46 female) diagnosed with acute STEMI and who underwent pPCI were retrospectively enrolled in the current study. The proportion of patients with diabetes mellitus was 27% in the study group, while 25% had hyperlipidemia, 52% were smokers, and 56% had hypertension. Approximately one-third of the patients underwent pPCI due to inferior MI (37.8%) and 29 patients (19%) experienced contrast-induced nephropathy after the pPCI. Two patients were hospitalized as cardiac arrest and resuscitated before the pPCI. Group 1 comprised 36 patients (24%) with a TIMI 3 flow (spontaneous reperfusion) before coronary intervention and 112 patients with a TIMI flow 0–2 made up Group 2.

Both groups were similar in terms of demographic characteristics and traditional risk factors. The SYNTAX and major adverse cardiac events (MACE; acute coronary syndrome, repeat target vessel revascularization, death, stroke) scores were significantly higher in Group 2 (p=<0.001, p=0.012; respectively). In laboratory analyses, the mean±SD of the 25(OH)D_3 level was significantly higher in Group 1 than in Group 2. (p=0.003) (Fig. 2) Serum troponin-I and creatinine levels were significantly higher in Group 2 (p<0.004, p=0.019, respectively). The mean LVEF was lower in Group 2 (p<0.001). The Killip class was more severe in Group 2 (p=0.006) than in Group 1. Demographic, angiographic, and laboratory characteristics of the study groups are provided in Table 1.

Age, Killip class, LVEF, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were correlated with the SYNTAX score, and 25(OH)D_3, troponin-I, C-reactive protein (CRP), and creatinine were weakly correlated with the SYNTAX score. Correlation analysis of study parameters with the SYNTAX score and 25(OH)D_3 are shown in Table 2 and Figure 1.

According to multilogistic regression analysis, the SYNTAX score (95% confidence interval [CI]: 0.678–0.853; p<0.001), Rentrop collateral (95% CI: 0.152–0.997; p=0.049), and troponin-I (95% CI: 0.905–0.981; p=0.004) levels were the most signifi-

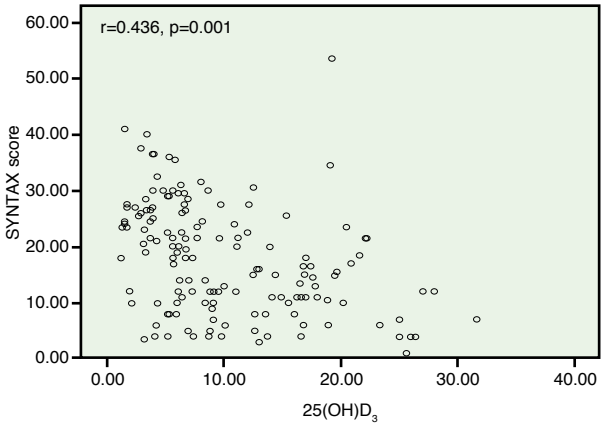

Figure 1. The correlation of 25(OH)D_3 level with SYNTAX score.

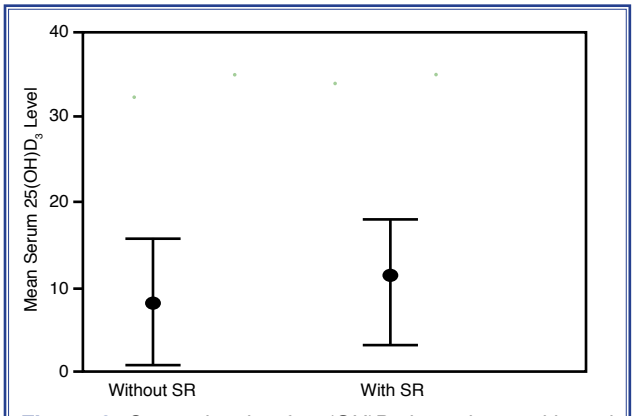

Figure 2. Serum levels of 25(OH)D_3 in patients with and without spontaneous reperfusion (SR).

Table 1. Demographic, angiographic, and laboratory characteristics of the study groups

Baseline characteristics	Group 1 (n=36)	Group 2 (n=112)	p
Age (years)	56.8±10.4	60.3±11.8	0.117
Gender-female, n (%)	8 (22)	38 (33)	0.187
Diabetes mellitus, n (%)	6 (17)	34 (30)	0.108
Hypertension, n (%)	19 (52)	64 (57)	0.646
Hyperlipidemia, n (%)	8 (22)	30 (27)	0.586
Smoking, n (%)	22 (61)	56 (50)	0.245
Angiographic characteristics			
Initiated symptom-door time (h)	2 (1–2.87)	2.5 (1.5–4)	0.82
Door-balloon time (min)	26.5±11.7	32.7±19	0.067
Myocardial infarction type-inferior/anterior/ posterolateral (%)	41/18/41	36/38/26	0.52/0.016/0.072
Synergy Between PCI with Taxus and Cardiac Surgery score	8.1±4.6	21.2±9.1	<0.001
Contrast induced nephropathy, n (%)	4 (11)	25 (22)	0.157
Previous cardiac arrest, n (%)	0 (0)	2 (1.7)	1.00
Stent type-Bare metal stent/drug eluting stent, n (%)	5/31 (13/86)	41/71 (36/64)	0.010/0.021
Stent length (mm)	21.4±5.7	24.3±7.4	0.032
Stent diameter (mm)	2.9±0.4	2.9±0.3	0.847
Post percutaneous coronary intervention diameter (mm)	3.2±0.4	3.1±0.4	0.364
Pre-dilatation, n (%)	12 (33)	75 (67)	<0.001
Post-dilatation, n (%)	10 (27)	34 (30)	0.768
Severe tortuosity, n (%)	0 (0)	4 (3.6)	0.572
Rentrop collateral degree	0.3±0.6	0.5±0.6	0.223
Vein graft intervention, n (%)	0 (0)	3 (2.7)	1.00
In hospital MACE, n (%)	0 (0)	16 (14.2)	0.012
In hospital mortality, n (%)	0 (0)	6 (5.3)	0.336
Stent thrombosis, n (%)	1 (2.7)	4 (3.6)	1.00
Laboratory parameters			
25-hydroxyvitamin D_3 (ng/L)	12.8±7	8.9±6.5	0.003
N-terminal pro-B-type natriuretic peptide (pg/mL)	75 (40–117)	283 (103–609)	<0.001
C-reactive protein (mg/dL)	0.37 (0.2–0.8)	0.75 (0.3–2.1)	0.009
Troponin-I (ng/mL)	7.2 (3.1–21.7)	25 (5.5–50)	0.004
Serum creatinine (mg/dL)	0.7±0.1	0.9±0.3	0.019
Total cholesterol (mg/dL)	176.6±35	178.1±42.5	0.845
High density lipoprotein (mg/dL)	36.9±11.9	39.5±10.5	0.212
Low density lipoprotein (mg/dL)	131.1±36.1	127.1±42.9	0.613
Serum glucose (mg/dL)	143.7±75.6	156.7±74.6	0.893
Hemoglobin (g/dL)	14±1.5	13.5±1.7	0.138
Mean platelet volume (fL)	8.8±2.4	8.3±1.7	0.179
Systolic blood pressure (mm Hg)	128.6±23.2	123.7±20.8	0.234
Diastolic blood pressure (mm Hg)	83.3±10.2	79.3±15.1	0.151
KILLIP class	1.1±0.4	1.5±0.7	0.006
Mean Left ventricular ejection fraction (%)	53±7	44.2±10.7	<0.001

Values are presented as mean±standard deviation or percentage. P<0.05 was accepted as significant. MACE= Major adverse cardiovascular event (acute coronary syndrome, repeat target vessel revascularization, dead, stroke).

Table 2. Correlation analysis results examining study parameters, Synergy between PCI with Taxus and Cardiac Surgery score, and 25-hydroxyvitamin D_3

	SYNTAX score	25-hydroxyvitamin D_3
Age (years)	0.291/<0.001	-0.265/0.001
Troponin-I (ng/mL)	0.204/0.013	-0.101/0.224
Low density lipoprotein (mg/dL)	0.04/0.964	0.067/0.421
Killip class	0.398/<0.001	-0.209/0.011
Left ventricular ejection fraction (%)	-0.526/<0.001	0.343/<0.001
N-terminal pro-B-type natriuretic peptide (pg/mL)	0.294/<0.001	-0.187/0.023
Systolic blood pressure (mm Hg)	-0.110/0.184	0.049/0.554
C-reactive protein (mg/dL)	0.178/0.03	-0.094/0.256
Glucose (mg/dL)	0.261/0.001	-0.151/0.06
Creatinine (mg/dL)	0.199/0.016	-0.086/0.297

P<0.05 was accepted as significant. SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery.

Table 3. Predictors of spontaneous reperfusion in univariate and multivariate logistic regression analysis

	Models			
	1	*p*	2	*p*
	OR (95% CI)		OR (95% CI)	
Age (years)	0.97 (0.94–1.007)	0.118	–	–
25-hydroxyvitamin D_3	1.080 (1.024–1.139)	0.005	–	–
Left ventricular ejection fraction (%)	1.095 (1.048–1.144)	<0.001	–	–
SYNTAX score	0.770 (0.701–0.847)	<0.001	0.760 (0.678–0.853)	<0.001
Rentrop collateral	0.343 (0.130–0.907)	0.014	0.388 (0.152–0.997)	0.049
KILLIP class	0.328 (0.140–0.769)	0.021	–	–
High density lipoprotein (mg/dL)	0.977 (0.943–1.013)	0.212	–	–
Troponin–I (ng/mL)	0.958 (0.935–0.981)	<0.001	0.942 (0.905–0.981)	0.004
Diabetes mellitus (%)	0.57 (0.228–1.444)	0.238	–	–

P values <0.25 were included in the second model; p<0.05 was accepted as significant in the second model.
CI: Confidence interval; OR: Odds ratio; SYNTAX: Synergy Between PCI with Taxus and Cardiac Surgery.

cant predictors of SR after variables with a p value less than 0.25 were included. (Table 3) Although $25(OH)D_3$ (95% CI: 0.991-1.185; p=0.079) and high--density lipoprotein (HDL) (95% CI: 0.893–1.001; p=0.055) were excluded in the second model, they could be accepted as borderline predictors of SR in our multilogistic regression analysis.

DISCUSSION

Our study indicates that $25(OH)D_3$ levels are higher in STEMI patients with SR. Moreover, strong correlations were detected between $25(OH)D_3$ level, age, Killip class, LVEF, and NT-proBNP. These results are, to the best of our knowledge, the first demonstration in the literature of a potential association between $25(OH)D_3$ and SR in STEMI patients.

SR is defined as the presence of a TIMI 3 flow in infarct-related artery before revascularization in STEMI patients, and it is associated with short-term clinical improvement.[17] The presence of SR alleviates in-hospital complications after STEMI. However, during long-term follow-up, comparable results were found between patients with and without SR. Zhu et al.[2] reported that SR was seen in 17.2% to 36.5% of STEMI patients. In the current study, SR was detected in 24%

of the patients. The absence of SR has been associated with a higher SYNTAX score, oxidative stress, and a higher Killip classification in a recent report.[18] Similarly, a significantly lower SYNTAX score and Killip class were detected in the SR group compared with Group 2 in our study. A significantly lower LVEF was also noted in the group without SR.

Li et al.[19] demonstrated that SR was more frequently seen in patients presenting with anterior MI and that the presence of SR was associated with a decreased need for stenting. Our results are consistent with those of Li et al., in some ways. We stented all of the patients who developed SR, and the mean stent length was greater in patients without SR relative to those with SR. The presence of SR was also associated with greater symptomatic improvement and fewer in-hospital complications. In contrast with the study results reported by Li et al., we detected a greater rate of anterior MI in the group without SR. These results demonstrate that better coronary blood flow before primary PCI in STEMI patients is associated with improved short-term results. While in-hospital mortality was not observed in the SR group, there was a 5.3% mortality rate in the non-SR group in the current study.

Very few studies have investigated an association between SR and chemical mediators in STEMI patients. Endothelin-1 is one of these mediators, and demonstrates vasoconstrictor effects through the action of a phospholipase enzyme. Higher levels of endothelin-1 were detected in STEMI patients without SR relative to those with SR.[20] In our study, higher levels of 25(OH)D_3 were found in STEMI patients with SR compared with those without SR. An 25(OH)D_3 deficiency was associated with slow filling of the distal coronary vascular bed.[21] Certain factors may influence the blood flow rate secondary to 25(OH)D_3 deficiency, and increase the risk of coronary artery disease. Among the causative factors that have been reported are an increased aldosterone level and its vasoconstrictor effect, and the development of hypertension related to a decreased 25(OH)D_3 level. Left ventricular hypertrophy secondary to hypertension may impair coronary circulation in addition to the vasoconstrictor effect of aldosterone.[22,23] The mechanism of action of vitamin D is mediated by cyclic guanosine monophosphate (cGMP) and treatment with vitamin D increases nitric oxide, and lowers high-sensitivity CRP levels.[24,25] Increased nitric oxide levels may lead to cGMP-mediated coronary vasodilation and increased coronary artery blood flow, which may explain the results of our study.[26] The anti-endothelin-1 effects of 25(OH)D_3, increased risk factors for coronary artery disease, inflammation, and atherosclerosis led us to investigate the effects, if any, of vitamin 25(OH)D_3 on SR.[27–29]

Vitamin 25(OH)D_3 deficiency not only decreases coronary artery blood flow but it is also associated with the severity of coronary artery disease. In a previous study, the severity of coronary artery disease in cases of stable coronary artery disease was evaluated using the SYNTAX score, and an association between a higher baseline SYNTAX score and lower vitamin 25(OH)D_3 values was demonstrated.[30] A significant negative correlation was also found between the 25(OH)D_3 level and SYNTAX score in the current study. Vitamin D deficiency has also been reported to increase in-hospital and long-term mortality, in addition to a having a correlation with the development of inflammation and coronary artery disease.[31] Therefore, the association between 25(OH)D_3 deficiency and progressive atherosclerosis and coronary artery risk factors should be assessed. A recent study strengthens this assertion, demonstrating the impact of vitamin D deficiency on HDL metabolism.[32] A lower vitamin D level was related to impaired proinflammatory polarization of macrophages and decreased the effect of "LXRs/ATP-binding membrane cassette transporter A1 (ABCA1)" protein, which plays a role in the formation of HDL. In our study, based on multivariate logistic regression analysis, a trend toward significance for both 25(OH)D_3 and HDL to predict the development of SR was observed. The SYNTAX score, presence of Rentrop collaterals, and troponin-I were determined to be independent predictors of SR.

Our findings demonstrating an association between 25(OH)D_3 and coronary artery blood flow patterns should be supported by larger-scale, prospective studies with long-term follow-up.

Study limitations

This study included a relatively small number of patients for a retrospective study. We could not examine the parathyroid hormone level of the patients. Furthermore, since it was a retrospective study, we couldn't analyze signal transduction pathways, such

as nitric oxide and secondary messengers, which could verify the effects of vitamin D on cardiac smooth muscle.

Conclusion

In conclusion, lower levels of 25(OH)D_3 may be associated with the absence of SR, increased disease severity, and in hospital MACE. Measurement of the level of 25(OH)D_3 could be included in the routine laboratory examination of patients with coronary artery disease, and more attention should be given to supplementation in cases of deficiency.

Ethics Committee Approval: This study was approved by the local ethics committee (date: 10/06/2016, number:54)

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: O.A., M.T.; Design: O.A., M.T., M.G., A.B., Ö.Ş.; Supervision: O.A., M.T., M.G., A.B.; Materials: O.A., H.K., H.H., M.K.; Data: F.Ö., H.K., H.H., Ö.Ş., M.K.; Analysis: M.T., F.Ö, M.G., M.K.; Literature search: O.A., A.B., F.Ö., H.K., H.H.; Writing: O.A., M.T., M.G., Ö.Ş.; Critical revision: O.A., M.T., Ö.Ş.

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Keywords: 25-hydroxyvitamin D3; coronary artery disease severity; coronary flow; myocardial infarction; spontaneous reperfusion.

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