ORIGINAL ARTICLE

Vitamin D is a predictor of ST segment resolution and infarct size following thrombolysis in patients with acute ST elevation myocardial infarction

D vitamini akut ST yükselmeli miyokart enfarktüsü olan hastalarda tromboliz sonrasında ST segment çözünürlüğünün ve enfarktüs boyutunun öngörülmesini sağlamaktadır

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ABSTRACT

Objective: Vitamin D (VitD) insufficiency is linked to various chronic conditions, including cardiovascular disease. Aim of the present study was to examine role of serum VitD in resolution of ST segment elevation (STR) in response to thrombolytic therapy following acute ST elevation myocardial infarction (STEMI).

Methods: VitD was measured prospectively in all consecutive patients who were admitted with STEMI and received thrombolysis during the calendar year of 2014. STR was defined as ≥50% decrease in initial magnitude of STR 90 minutes after treatment. Multivariate binary logistic regression analysis was performed to identify effect of confounding variables on STR.

Results: Average age was 58±14 years in 227 patients (41 female and 186 male). Total of 24.7% of patients had sufficient VitD (>30 ng/mL), whereas 46.2% had VitD insufficiency (10–30 ng/mL), and remaining 29.1% had VitD deficiency (<10 ng/mL). Significant STR occurred in 57.3% of the patients. In a nonlinear pattern, serum VitD concentration directly correlated with likelihood of STR (p=0.012). VitD deficient patients had larger enzymatic infarct size compared with those with sufficient VitD (p=0.026). In multivariate logistic regression analysis, while diabetes doubled (p=0.033) and involvement of anterior wall created 2.7-fold increase in probability of non-resolution (p=0.001), for every unit increase in serum VitD, likelihood of STR increased by 2.1% (p=0.023).

Conclusion: VitD deficiency in patients with STEMI was associated with lower occurrence of STR and larger enzymatic infarct size in response to thrombolytic therapy.

ÖZET

Amaç: D vitamin (VitD) yetersizliği kalp-damar hastalıklarını da içeren birçok kronik hastalıkla bağlantılıdır. Akut ST yükselmeli miyokart enfarktüsü (STYMİ) sonrasında trombolitik tedaviye yanıt olarak gelişen ST segment yükselmesinin çözünürlüğünde (STR) serumdaki D vitamininin rolünü incelemeyi amaçladık.

Yöntemler: 2014 takvim yılı içerisinde STYMİ geçirerek başvurmuş ve tromboliz tedavisi almış olan her bir hastanın hastalık geçirdikleri sıradaki VitD seviyeleri ileriye yönelik olarak ölçüldü. STR, tedavi sonrasındaki ilk 90 dakikadaki ST yükselmesi ≥%50 azalma olarak tanımlandı. Çelişkili (kompleks) değişkenlerin STR üzerindeki etkisini belirlemek için çok değişkenli ikili lojistik regresyon analizi yapıldı.

Bulgular: Çalışmaya dahil edilen 227 hastanın (41 kadın ve 186 erkek) yaş ortalamaları 58±14 idi. Hastalardan %24.7'si yeterli miktarda VitD (>30 ng/mL) sahipken,%46.2'sında VitD yetersizliği (<10 ng/mL), geriye kalan hastalarda ise (%29.1) VitD eksikliği vardı (<10 ng/mL). Hastaların %57.3'ünde belirgin STR meydana gelmişti. Doğrusal olmayan bir modele göre, serum VitD konsantrasyonu doğrudan STR gerçekleşme olasılığı ile korelasyon gösterdi (p=0.012). VitD eksikliği olan hastalarda enzimatik enfarktüs büyüklüğü, yeterli miktarda VitD olan hastalara göre daha büyüktü (p=0.026). Çok değişkenli lojistik regresyon analizine göre, diyabet çözünmezlik olasılığını iki katına çıkarırken (p=0.033), ön duvardaki tutulumu ise çözünmezlik olasılığını 2.7 kat artırmaktaydı (p=0.001). Serum VitD düzeylerindeki her bir birimlik artış ST segment çözünürlüğü olasılığını %2.1 (p=0.023) oranında arırmaktaydı.

Sonuç: ST yükselmeli miyokart enfarktüsü geçirmiş hastalardaki VitD eksikliği trombolitik tedaviye yanıt olarak daha düşük STR frekansı ve daha geniş enzimatik enfarktüs boyutlarıyla ilişkilidir.

Received: January 18, 2017 *Accepted:* March 27, 2017

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Inadequate vitamin D (VitD) level is considered to be a global health problem, as it currently affects over 1 billion people, worldwide.[1] With the identification of VitD receptors on almost all cells of various human tissues, including vascular smooth muscle, endothelium, and cardiomyocytes, a pluripotential function has been described for VitD, in addition to its main role in bone-mineral metabolism.[2] An association between VitD insufficiency (serum level <30 ng/mL) and various chronic conditions, such as neoplasms, autoimmune disorders, hypertension, diabetes, coronary artery disease, and heart failure has been reported.[3,4] In a large prospective cohort, after controlling for traditional contributing factors, risk of ST elevation myocardial infarction (STEMI) was higher among men with insufficient levels of VitD.[5] In a fairly recent meta-analysis, there was graded inverse relationship between VitD and risk of coronary heart disease.[6] Though an exact cause-effect correlation has yet to be shown between hypovitaminosis D and atherosclerosis, there are several plausible mechanisms, including dysregulation of renin-angiotensin-aldosterone system (RAAS). As negative regulation of renin gene transcription by VitD is reduced, elevated RAAS activity leads to progression of atherogenic processes and negative myocardial remodeling.[7] Moreover, development of insulin resistance, inflammatory cytokine proliferation, and associated increased thrombogenicity may be potential contributors to higher cardiovascular risk in individuals with low VitD level.[2,8]

Abbreviations:

ECG	*Electrocardiography*
CK	*Creatine kinase (CK)*
CK-MB	*Creatine kinase MB fraction*
cTnI	*Cardiac troponin I*
HsCRP	*High sensitivity C-reactive protein*
MACCE	*Major adverse cardiac and cerebrovascular event*
MMP	*Matrix metalloproteinase*
PAI-1	*Plasminogen activator inhibitor-1*
RAAS	*Renin-angiotensin-aldosterone system*
ROC	*Receiver operating characteristic*
STEMI	*ST elevation myocardial infarction*
STR	*ST segment elevation*
VitD	*Vitamin D*

Significant resolution of ST segment elevation (STR) in patients with acute STEMI has been associated with smaller infarct size, better preservation of left ventricular function, and favorable clinical outcome.[9] STR is considered a surrogate for reperfusion of cardiac myocytes.[10,11] Although enough evidence exists to support higher probability of acute STEMI in clinically VitD deficient patients, to our knowledge, there has been no study examining the efficacy of thrombolytic therapy and clinical outcome of patients following an established STEMI in relation to their serum VitD concentration. Objective of this study was to evaluate association between serum VitD level and outcome of acute STEMI in patients treated with thrombolysis. Primary endpoint of this research was STR. It was hypothesized that patients with insufficient or deficient levels of VitD would demonstrate less likelihood for STR following thrombolytic therapy for acute STEMI.

METHODS

Study design

This was a prospective, observational study examining VitD level and its association with STR in patients with STEMI. The study protocol was reviewed by the institutional ethics committee at Tabriz University of Medical Sciences and scientific merits were approved. The study was conducted between January 2014 and January 2015 at university-affiliated heart hospital. Patients presenting with acute STEMI within 12 hours of onset of their symptoms who received thrombolytic as reperfusion strategy were considered for enrollment. Decision to administer thrombolytic was made by the managing cardiologist. Patients with chronic kidney disease and estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2, those with paced rhythm and pre-existing left bundle branch block, and those taking VitD supplement were excluded from the study. Additionally, patients were not considered if they were younger than 18 years of age, if they presented more than 12 hours from symptom onset, or if they had contraindication to receive thrombolytic. The study was performed in compliance with the Declaration of Helsinki and informed consent was obtained from participants upon enrollment. Demographic details; comorbidities; electrocardiography (ECG), laboratory, and echocardiography findings; as well as coronary angiography findings (if performed during the course of index hospitalization) were recorded for each case.

Electrocardiographic analysis

Initial ECG was recorded upon arrival to the emergency room and was considered baseline ECG. STEMI was defined according to universal definition of myocardial infarction[12] in the presence of new ST elevation from J point in 2 contiguous leads of ≥0.1

mm in all leads except for leads V2 and V3 for which ≥0.2 was considered significant. Lead with maximal ST elevation was identified and extent of ST elevation was measured and used as reference to evaluate STR. amount of ST elevation in the same lead was assessed 90 minutes after administering thrombolytic treatment. STR was calculated. Patients with ≥50% resolution of initial maximal ST elevation were assigned to (+)STR group, and those with <50% resolution of initial maximal ST elevation were allocated to (-)STR group.

Laboratory analyses

Venous blood was drawn upon presentation before receiving any treatment. After blood was collected, samples were centrifuged, and extracted serum stored at -70°C until 25-hydroxy vitamin D concentrations (VitD) was measured with fully automated chemiluminescent immunoassay (LIASON 25 OH Vitamin D TOTAL Assay; DiaSorin SpA, Saluggia, Italy) on the automated LIAISON analyzer (DiaSorin SpA, Saluggia, Italy). Cardiac enzymes, including total creatine kinase (CK) (IU/L), creatine kinase MB fraction (CK-MB) (IU/L), and cardiac troponin-I (cTnI) (μg/L) were measured upon presentation. Serial measurement of cardiac enzymes was performed. Second set of cardiac enzymes was measured 8 to 12 hours after presentation, and third set was measured after 24 hours for CK-MB and after 48 hours for cTnI. All blood samples were analyzed at central core laboratory. Area under the curve for serial measurements of CK-MB using standard trapezoidal method was considered surrogate for enzymatic infarct size.

Definitions

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or current use of antihypertensive medications. Diabetes was defined as fasting blood glucose of ≥126 mg/dL or current use of glucose-lowering medications. Hyperlipidemia was defined as total cholesterol of ≥200 mg/dL in the previous 6 months prior to admission. Family history of premature ischemic heart disease was accepted if there was history of coronary heart disease at age of onset <55 years for men and <65 years for women in first-degree family members. VitD level below 10 ng/mL was considered deficient, whereas level of 10 to 30 ng/mL was considered insufficient. VitD level above 30 ng/mL was considered sufficient. Major adverse cardiac and cerebrovascular event (MACCE) was defined as composite rate of recurrent ischemia, stroke, heart failure, or death during hospitalization.

Sample size determination

Since there was no similar previous study examining VitD level and STR, first 100 patients were used as pilot project for sample size determination. Mean difference in VitD level was 8 ng/mL in patients with and without STR. Therefore, required sample size with alpha error of 0.05 and power of 0.80 was 56 patients in each group. With 227 patients enrolled, power of 0.96 with 95% confidence interval was achieved in the present study.

Treatment protocol

Accelerated streptokinase regimen was administered as described previously: 1,500,000 units of streptokinase was dissolved in 50 mL of saline and infused over 30 minutes using infusion pump through peripheral vein.[13]

Statistical analysis

All data obtained were analyzed using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was performed to test normality of distribution for continuous variables. If normality was rejected, data were analyzed using non-parametric test of Mann-Whitney U test when comparing 2 groups, and Kruskal-Wallis one-way analysis of variance (ANOVA) (k samples) for 3 groups. Continuous variables were reported as mean±SD in case of normal distribution, or median and interquartile range when normality was not present. Categorical variables were presented as frequency (percentage), and Fisher's exact test or chi-square test with Yates's correction was used for comparison, as appropriate. Comparison of continuous variables between study groups was performed with use of independent t-test or ANOVA as needed. Multivariate binary logistic regression model was designed to study independent predictors of STR using variables with p value of less than 0.10 in univariate analysis. Additionally, receiver operating characteristic (ROC) curve was plotted to establish cut-off value for vitamin D in predicting STR. P<0.05 was regarded as statistically significant.

RESULTS

Total of 227 patients (41 women) were enrolled in this study. Mean age of the study group was 58±14 years, and ranged between 31 and 87 years. In all, 121 (53.3%) patients had anterior STEMI, whereas remaining 106 (46.7%) had inferior STEMI. In terms of comorbidities, 18.9% were diabetic, 37.9% were hypertensive, 15.4% had hyperlipidemia, and 46.7% were current/past smokers. Coronary angiography was performed in 175 (77.1%) of patients during the course of index hospitalization. Among these patients, 7 (4%) had non-significant coronary artery obstruction, 85 (48.6%) patients had significant stenosis in single coronary artery, 45 (25.7%) had significant stenosis in 2 coronary arteries, and 38 (21.7%) patients had significant stenosis in all 3 coronary arteries.

Serum VitD level was sufficient in 56 (24.7%) patients, whereas 105 (46.2%) patients had VitD insufficiency, and 66 (29.1%) patients had VitD deficiency. Mean VitD was 22.9±18.3 ng/mL. STR >50% (primary outcome variable) occurred in 130 (57.3%) members of the study population and MACCE (secondary outcome variable) occurred in 36 (15.9%) of the patients. One patient died during hospitalization. Table 1 illustrates characteristics of (+)STR group in comparison with (-)STR group. VitD level was significantly lower in patients in (-)STR group.

Table 2 provides characteristics of patients according to status of serum VitD level. Patients with VitD deficiency were comparable to the rest of the study population in terms of comorbidities, yet they had significantly lower percentage of STR following thrombolysis. They also had larger infarct size, as assessed by cardiac enzyme release. Dunn-Bonferroni post hoc analysis indicated that for enzymatic infarct size based on CK-MB, there was significant difference between patients with normal VitD level and those with level

Table 1. Patient characteristics according to occurrence of ST resolution on electrocardiogram

	STR (+) (n=130)	STR (–) (n=97)	*p*
Age (years)	59±14	57±13	0.273
Gender (female/male)	23/107	18/79	0.867
Myocardial infarction location (anterior/inferior)	57/73	64/33	0.001
Familial history of premature coronary artery disease, n (%)	7 (5.4)	3 (3.1)	0.522
Diabetes mellitus, n (%)	19 (14.6)	24 (24.7)	0.043
Hypertension, n (%)	49 (37.7)	37 (38.1)	0.945
Hyperlipidemia, n (%)	24 (18.5)	11 (11.3)	0.199
Smoking (current or past), n (%)	59 (45.4)	47 (48.5)	0.745
Prior coronary artery disease, n (%)	5 (3.8)	1 (1.0)	0.242
Creatine kinase-MB 1 (U/L)	33 (28)	46 (49)	0.028
Creatine kinase-MB 2 (U/L)	107 (145)	145 (182)	0.040
Creatine kinase-MB 3 (U/L)	54 (55)	78 (66)	0.006
Cardiac troponin-I 1 (μg/L)	0.2 (1.6)	0.2 (2.6)	0.897
Cardiac troponin-I 2 (μg/L)	8.9 (16.7)	13.5 (23.5)	0.005
Cardiac troponin-I 3 (μg/L)	4.7 (6.5)	7.4 (13.2)	0.001
Vitamin D (ng/mL)	21.4 (22.7)	17.1 (19.2)	0.037
Area under the curve creatine kinase-MB (U/L *24 hour)	2038 (2382)	2728 (2872)	0.013
Area under the curve cardiac troponin-I (ng/mL *24 hour)	158 (252)	327(371)	0.008
Left ventricular ejection fraction (%)	43.2±7.4	38.8±7.7	<0.001
Length of stay (days)	5.0±1.3	5.5±2.0	0.023
Major adverse cardiac and cerebrovascular events, n (%)	17 (13.1)	19 (19.6)	0.252

STR: ST-segment elevation.

Table 2. Characteristics of each group according to vitamin D status

	Vitamin D >30 ng/mL (n=57)	Vitamin D 10–30 ng/mL (n=104)	Vitamin D <10 ng/mL n=66	*p*
Age (years), Mean±SD	62±15*	58±13	55±14*	0.048
Percentage of ST resolution	63 (42)	50 (43)	43 (47)	0.126
Creatine Kinase-MB on admission (IU/L)	31 (38)	36 (33)	35 (40)	0.745
Cardiac troponin-I on admission (ng/mL)	0.2 (1.1)	0.2 (2.8)	0.3 (1.3)	0.285
Creatine kinase total on admission (IU/L)	232 (312)	222 (390)	225 (332)	0.986
Maximal ST elevation on admission (mm)	4 (4)	4 (12)	4 (11)	0.567
Maximal ST elevation after thrombolysis (mm)	1.5 (3.0)	2.0 (2.0)	2.0 (3.0)	0.417
Area under the curve for creatine kinase-MB (IU/L*24 hrs)	1780 (2186)	2326 (2321)	2734 (3168)	0.030
Area under the curve for cardiac troponin-I (μg/L*48 hrs)	133 (242)	203 (323)	318 (321)	0.007
Left ventricular ejection fraction (Percent)	42±8	42±8	40±8	0.137
Length of stay (days)	5.5±1.7	5.2±1.9	5.1±1.1	0.404
Gender (M/F)	44/13	88/16	54/12	0.561
Diabetes mellitus, n (%)	7 (12.3)	24 (23.1)	12 (18.2)	0.243
Hypertension, n (%)	27 (47.4)	39 (37.5)	20 (30.3)	0.150
Smoking, n (%)	21 (36.8)	49 (47.1)	36 (54.5)	0.145
Hyperlipidemia, n (%)	6 (11.8)	21 (20.2)	8 (12.1)	0.181
Family history of premature CAD, n (%)	4 (7.0)	4 (3.8)	2 (3.0)	0.523
Prior coronary artery disease, n (%)	2 (3.5)	4 (3.8)	0 (0)	0.280
Normal coronary, n (%)	2 (4.9)	5 (6.3)	0 (0)	
1 vessel disease, n (%)	28 (68.3)	26 (32.5)	31 (57.4)	
2 vessel disease, n (%)	4 (9.8)	27 (33.8)	14 (25.9)	0.459
3 vessel disease, n (%)	7 (17.1)	22 (27.5)	9 (16.7)	
Major adverse cardiac and cerebrovascular events, n (%)	12 (21.0)	15 (14.4)	9 (13.6)	0.115
Lack of ST resolution, n (%)	19 (33.3)	43 (41.3)	35 (53.0)	0.082

Asterisks denote variables that were significant in post hoc analysis. SD: Standard deviation.

below 10 ng/mL (p=0.026). However, difference between patients with normal VitD level and those with VitD insufficiency, or those with insufficient versus deficient VitD level was not statistically significant (p=0.463 and 0.083, respectively).

As for cumulative release of cTn-I, there was significant difference between patients with normal VitD level and those with level below 10 ng/mL (p=0.003), and also between patients with normal VitD level and those with VitD insufficiency (p=0.010). However, difference between those with insufficient versus deficient VitD level was not statistically significant (p=0.146).

Left ventricular ejection fraction and hospital length of stay were not affected by VitD level. Multivariate binary logistic regression model was constructed to identify independent contributors to lack of STR, including all variables with p value less than 0.10 in univariate analyses. Consequently, involvement of the anterior wall in myocardial infarction zone (p=0.001) and diabetes mellitus (p=0.033) were included in this model in addition to serum VitD level as the only covariates (Table 3). According to this model, for every 1 ng/mL increment of VitD, there was 2.1% increase in likelihood of positive response to thrombolytic therapy. In order to examine predictive value of serum VitD for STR in response to post-STEMI thrombolysis, ROC curves were plotted with appropriate coordinates (Figure 1). Area under

Table 3. Multivariate binary logistic regression for the lack of ST resolution with the effect of confounding variables of diabetes mellitus, location of myocardial infarction, and serum vitamin D concentration

	Coefficient	SE	P value	Odds ratio	95% Confidence interval	
					Lower	Upper
Diabetes mellitus	0.771	0.362	0.033	2.16	1.064	4.396
Serum vitamin D level	-0.021	0.009	0.023	0.98	0.961	0.997
Anterior/inferior wall MI	0.987	0.289	0.001	2.68	1.524	4.725
Constant	-0.518	0.304	0.088	0.596		

MI: Myocardial infarction; SE: Standard error.

the curve for this plot was 0.59±0.04 with p value of 0.017. Cut-off value of serum VitD concentration in predicting STR was 20 ng/mL. However, sensitivity of serum VitD level of 20 ng/mL in predicting STR was 55% and specificity was 62%.

DISCUSSION

Prevalence of VitD insufficiency/deficiency is very high in our patient population with STEMI, with frequency comparable to that of previous studies.[14,15] In the present study, results demonstrated that lower VitD level is associated with greater risk of failure to respond to thrombolysis, and thereby results in larger enzymatic infarct size in patients admitted with STEMI. To the best of our knowledge, this is the first study to address links between low VitD level and less response to thrombolytic therapy in STEMI. Lower response rate to thrombolysis translates into larger myocardial loss, and subsequently, less favorable outcome in follow-up. In this study, we have reported greater enzymatic release in patients with deficient level of VitD compared with patients with normal VitD level following STEMI event.

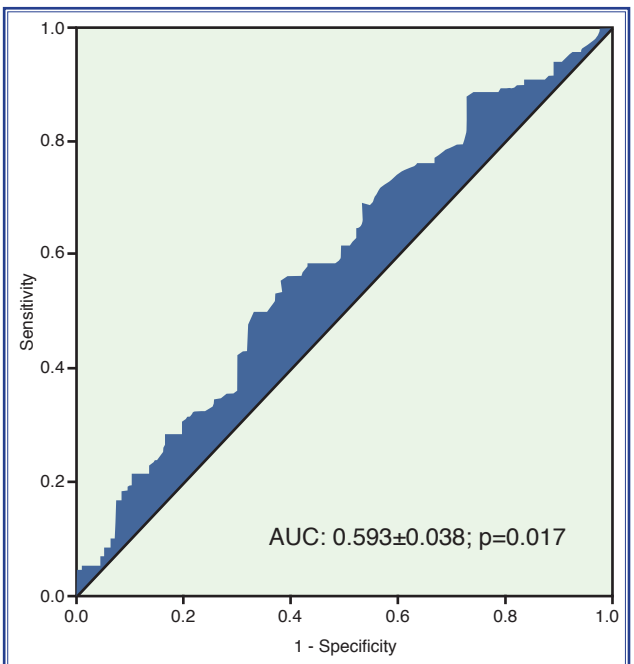

Figure 1. Receiver operating characteristic curve was plotted to establish the cut-off point for vitamin D in predicting ST segment elevation (STR) in response to thrombolysis in acute ST elevation myocardial infarction. Vitamin D with a cut-off value of 20 ng/mL predicted STR with sensitivity of 55% and specificity of 62%. (Area under curve 0.59±0.04).

VitD deficiency is an emerging risk factor for cardiovascular disease and it is implicated in maintaining vascular health. Over a period of 10 years in a longitudinal study, men with VitD insufficiency developed myocardial infarction more frequently than those whose vitamin level was normal. The association exists even after adjusting for traditional risk factors.[5] It has been reported that after acute myocardial infarction, heart failure is more frequently seen in patients with VitD deficiency than in those with adequate level of VitD.[14] That study included both STEMI and non-STEMI, and did not comment on reperfusion strategies.

Among proposed mechanisms that may explain the association between low level of VitD and cardiovascular disease, one may name the anti-inflammatory properties of this vitamin and its regulatory effects on renin expression.[8,16] Modulatory effects of VitD on RAAS are mediated through calcium-independent suppression of renin gene transcription. Moreover, studies show that in knockout mice for VitD receptors, renin expression increases and subsequently augments angiotensin II level, which subsequently leads to hypertension and left ventricular hypertrophy.[16]

Ventricular remodeling secondary to excessive RAAS activity particularly predisposes the myocardium to ischemia.

VitD has anti-inflammatory role, and deficiency promotes systemic and vascular inflammation. Balance between matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases, is a major contributor to local inflammatory reaction and initiation of coagulation cascade. Additionally, imbalance between proinflammatory and anti-inflammatory proteins in the myocardium is believed to play major role in ventricular remodeling.[17] Plasma concentration of MMP9 and high sensitivity C-reactive protein (hs-CRP) have been higher in patients with coronary artery disease than that of controls with no coronary atherosclerotic diseases.[18] Remarkably, VitD has been identified as an independent determinant of serum levels of hs-CRP and MMP9, which may provide an explanation for presence of local inflammation at the level of intima, tissue damage, and progression of atherogenesis.[19]

The net effect of VitD in homeostasis between procoagulant and anticoagulant states favors inhibition of clot formation and lysis of the formed clot. Thrombomodulin is an endogenous antithrombotic protein. Its expression is upregulated by VitD, while expression of tissue factor in monocytes (major coagulation factor that initiates the extrinsic pathway) is reduced by VitD.[20] Positive correlation has also been described between VitD and plasma level of tissue factor pathway inhibitor, which is a crucial inhibitor of coagulation.[21] Inadequacy of VitD correlated with occurrence of idiopathic deep vein thrombosis in another study.[22]

Moreover, profibrinolytic effects have been described for VitD by both in vivo and in vitro studies. Elevated plasminogen activator inhibitor-1 (PAI-1) level after thrombolytic therapy correlated with poor reperfusion of the occluded vessels in STEMI.[23] Jorde et al. reported significant and inverse relationship between VitD and tissue plasminogen activator, PAI-1 antigen level, and hs-CRP level in healthy subjects.[24] In another study, synthetic analogues of VitD were capable of inhibiting genetic expression of PAI-1 and its protein synthesis.[25] A localized and controlled fibrinolysis is the cornerstone of thrombolytic therapy, and therefore modulation of plasminogen activity is the most probable underlying mechanism through which VitD may have affected process of thrombolysis in the current study. Such observations call for further studies focused on hemostatic abnormalities observed in patients with VitD deficiency.[26]

Furthermore, VitD level inversely correlates with burden of vascular calcification.[27] In another in vitro study, effect of VitD on reducing platelet activation was demonstrated.[28] Greater degree of plaque calcification can potentially affect efficacy of thrombolytic in restoring coronary flow. All these factors may contribute to observed relative resistance to thrombolytic therapy in STEMI patients with reduced VitD level. Frequency and extent of STR in the present study are similar to those previously reported by our center.[29,30] STR after reperfusion treatment by primary percutaneous coronary intervention or thrombolysis offers crucial prognostic information in the setting of STEMI,[31] and has been shown to be of significant utility in both clinical practice and research.[32] The findings of the current study have clinical implications, as patients with known VitD inadequacy may not benefit as much from thrombolytic treatment in the setting of STEMI. Further studies addressing the outcome of primary percutaneous intervention in patients with vitamin D inadequacy are warranted.

The study is subject to some limitations. U-shaped relationship between VitD and outcome has been proposed, with both higher and lower levels associated with higher mortality.[33] However, there were only 5 patients in this series with VitD exceeding normal level, which is too few to examine this concept. We do not correlate extent of coronary artery disease or plaque burden with serum concentration of this vitamin. Additional confounding factors, which could affect occurrence of STR, may have been overlooked. Additionally, this study lacks any follow-up information post discharge from hospital.

Conclusion

VitD deficiency in patients with STEMI is associated with lower frequency of STR and larger enzymatic infarct size in response to thrombolytic therapy. Though lower VitD level is associated with lower efficacy of thrombolytic therapy in this study, whether vitamin D supplements could affect the outcome, and whether lower VitD level would correlate with long-term adverse events following episode of STEMI remain areas for further research.

Conflict-of-interest: None declared

REFERENCES

1. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080S–6S.
2. Mandarino NR, Júnior Fd, Salgado JV, Lages JS, Filho NS. Is vitamin d deficiency a new risk factor for cardiovascular disease? Open Cardiovasc Med J 2015;9:40–9. [CrossRef]
3. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81. [CrossRef]
4. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76–89. [CrossRef]
5. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80. [CrossRef]
6. Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol 2012;32:2794–802. [CrossRef]
7. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol 2004;89-90:387–92. [CrossRef]
8. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol 2008;52:1949–56. [CrossRef]
9. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol 2001;38:1283–94. [CrossRef]
10. van't Hof AW, Liem A, de Boer MJ, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial infarction Study Group. Lancet 1997;350:615–9. [CrossRef]
11. Sezer M, Nisanci Y, Umman B, Yilmaz E, Olcay A, Erzengin F, et al. New support for clarifying the relation between ST segment resolution and microvascular function: degree of ST segment resolution correlates with the pressure derived collateral flow index. Heart 2004;90:146–50. [CrossRef]
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35. [CrossRef]
13. Ghaffari S, Kazemi B, Golzari IG. Efficacy of a new accelerated streptokinase regime in acute myocardial infarction: a double blind randomized clinical trial. Cardiovasc Ther 2013;31:53–9. [CrossRef]
14. Ng LL, Sandhu JK, Squire IB, Davies JE, Jones DJ. Vitamin D and prognosis in acute myocardial infarction. Int J Cardiol 2013;168:2341–6. [CrossRef]
15. Aleksova A, Belfiore R, Carriere C, Kassem S, La Carrubba S, Barbati G, et al. Vitamin D Deficiency in Patients with Acute Myocardial Infarction: An Italian Single-Center Study. Int J Vitam Nutr Res 2015;85:23–30. [CrossRef]
16. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229–38.
17. Spinale FG. Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ Res 2002;90:520–30.
18. Muzzio ML, Miksztowicz V, Brites F, Aguilar D, Repetto EM, Wikinski R, et al. Metalloproteases 2 and 9, Lp-PLA(2) and lipoprotein profile in coronary patients. Arch Med Res 2009;40:48–53. [CrossRef]
19. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002;95:787–96. [CrossRef]
20. Koyama T, Shibakura M, Ohsawa M, Kamiyama R, Hirosawa S. Anticoagulant effects of 1alpha,25-dihydroxyvitamin D3 on human myelogenous leukemia cells and monocytes. Blood 1998;92:160–7.
21. Topaloglu O, Arslan MS, Karakose M, Ucan B, Ginis Z, Cakir E, et al. Is there any association between thrombosis and tissue factor pathway inhibitor levels in patients with vitamin D deficiency? Clin Appl Thromb Hemost 2015;21:428–33.
22. Khademvatani K, Seyyed-Mohammadzad MH, Akbari M, Rezaei Y, Eskandari R, Rostamzadeh A. The relationship between vitamin D status and idiopathic lower-extremity deep vein thrombosis. Int J Gen Med 2014;7:303–9.
23. Paganelli F, Alessi MC, Morange P, Maixent JM, Lévy S, Vague IJ. Relationship of plasminogen activator inhibitor-1 levels following thrombolytic therapy with rt-PA as compared to streptokinase and patency of infarct related coronary artery. Thromb Haemost 1999;82:104–8.
24. Jorde R, Haug E, Figenschau Y, Hansen JB. Serum levels of vitamin D and haemostatic factors in healthy subjects: the Tromsø study. Acta Haematol 2007;117:91–7. [CrossRef]
25. Wu-Wong JR, Nakane M, Ma J. Vitamin D analogs modulate the expression of plasminogen activator inhibitor-1, thrombospondin-1 and thrombomodulin in human aortic smooth muscle cells. J Vasc Res 2007;44:11–8. [CrossRef]
26. Targher G, Pichiri I, Lippi G. Vitamin D, thrombosis, and hemostasis: more than skin deep. Semin Thromb Hemost 2012;38:114–24. [CrossRef]
27. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997;96:1755–60. [CrossRef]
28. Stach K, Kälsch AI, Nguyen XD, Elmas E, Kralev S, Lang S, et al. 1α,25-dihydroxyvitamin D3 attenuates platelet activa-

tion and the expression of VCAM-1 and MT1-MMP in human endothelial cells. Cardiology 2011;118:107–15. [CrossRef]

29. Ghaffari S, Pourafkari L, Javadzadegan H, Masoumi N, Jafarabadi MA, Nader ND. Mean platelet volume is a predictor of ST resolution following thrombolysis in acute ST elevation myocardial infarction. Thromb Res 2015;136:101–6. [CrossRef]
30. Ghaffari S, Pourafkari L, Sepehrvand N, Aslanabadi N, Faridi L, Tajlil A, et al. Red cell distribution width is a predictor of ST resolution and clinical outcome following thrombolysis in acute ST elevation myocardial infarction. Thromb Res 2016;140:1–6. [CrossRef]
31. Schröder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. Circulation 2004;110:e506–10. [CrossRef]
32. Jones JB, Docherty A. Non-invasive treatment of ST elevation myocardial infarction. Postgrad Med J 2007;83:725–30.
33. Amrein K, Quraishi SA, Litonjua AA, Gibbons FK, Pieber TR, Camargo CA Jr, et al. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. J Clin Endocrinol Metab 2014;99:1461–9. [CrossRef]

Keywords: Myocardial infarction; ST resolution; thrombolysis; vitamin D.

Anahtar sözcükler: Miyokart enfarktüsü; ST çözünürlüğü; tromboliz; D vitamini.