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The influence of plasma 25-(OH) vitamin D levels in acute ST elevation myocardial infarction

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Abstract

Background: *The preventive role of acute occurring of collateral circulation (AOCC) to infarct related artery (IRA) in patients presenting with acute ST-segment elevation myocardial infarction (STEMI) is well known. Therefore, we aimed to investigate whether there is an association between admission plasma 25-hydroxyvitamin D (25(OH)D3) levels and grade of collateralization in patients with STEMI.*

Methods: *We prospectively included 369 STEMI patients within the first 12 h of symptoms onset. Patients were divided into two groups according to their Rentrop collateralization grade to IRA: poorly developed collateral (PDC) group (Rentrop grade ≤ 1, 272 patients) and well developed collateral (WDC) group (Rentrop grade ≥ 2, 97 patients).*

Results: *We observed that AOCC grade to IRA was negatively correlated with high sensitive C-reactive protein (hs-CRP), N terminal pro-B-type natriuretic peptide (NT-proBNP), as well as peak troponin T levels, yet positively correlated with admission plasma 25(OH)D3 level ($p < 0.05$, for all). In multivariate analysis, 25(OH)D3 levels (OR 1.246, 95% CI 1.185–1.310, $p < 0.001$), together with hs-CRP, NT-proBNP, and peak troponin T levels were found independent predictors of AOCC to IRA in patients with acute STEMI.*

Conclusions: *Admission level of plasma 25(OH)D3 levels together with cardiac risk biomarkers (troponin T, NT-proBNP, hs-CRP) are associated with collateralization grade to IRA in acute STEMI patients. In addition, 25(OH)D3 may be a promoter of AOCC in patients with acute STEMI.* (Cardiol J 2017; 24, 6: 677–684)

Key words: 25-(OH) vitamin D, ST-segment elevation myocardial infarction, collateral development, arteriogenesis

Introduction

Coronary collaterals are anastomotic conduits that can provide an alternative source of blood supply to jeopardized myocardium by acutely or chronically developed occlusive coronary artery disease [1, 2]. Acute occurring of coronary collateral circulation (AOCC) to infarct related artery (IRA) territory after onset of acute ST-segment elevation myocardial infarction (STEMI) has shown various beneficial effects on infarct size, ventricular function, microvascular circulation, hemodynamic status, and mortality [3–5]. In addition, existence of a chronic total occlusion (CTO) is another important process which leads to coronary collateral development. These chronically occurring collaterals to CTO also have various protective effects on myocardial viability, remodeling, and cardiovascular outcomes [6, 7].

Vitamin D is a steroidal hormone and plays a crucial role in various metabolic pathways, particularly in cardiovascular system. Epidemiological studies have shown an independent relationship between low vitamin D levels and cardiovascular risk factors (hypertension, diabetes mellitus, metabolic syndrome), cardiac events (myocardial infarction, congestive heart failure), and mortality [8–11]. In addition, the evidence suggests that

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there is a positive correlation between serum vitamin D levels and the development of collateral vessels to a totally occluded artery [12, 21]. Furthermore, the effect of serum vitamin D levels on collateralization grade of CTO artery has been established, and a positive correlation was observed [12, 13]. To the best of our knowledge, the effect of plasma 25-hydroxyvitamin D (25(OH)D3) levels on acute collateralization grade to IRA has not yet been studied. Accordingly, we aimed to investigate whether there is a relationship between admission plasma 25(OH)D3 levels and AOCC to the IRA in patients with acute STEMI.

Methods

Study population

In this prospective study, we enrolled 369 acute STEMI patients who underwent primary percutaneous coronary intervention (PCI) between May 2015 and November 2015. We included patients with symptoms of ischemic chest pain (at least for 30 min, and no longer than 12 h), and an electrocardiography (ECG) showing ST-segment elevation of 0.1 mV in two or more limb leads, or 0.2 mV in two or more contiguous precordial leads, or presumed new left bundle branch block. Angiographic evaluation of IRA and non-IRA was performed before primary PCI by two experienced cardiologists who were blinded to the study data. Rentrop collateral classification was used for grading AOCC to IRA territory on angiography. Rentrop classification was defined as follows: grade 0: no visible filling of any collateral channel; grade 1: filling of the side branches of the occluded artery, with no dye reaching the epicardial segment; grade 2: partial filling of the epicardial vessel; and grade 3: complete filling of epicardial vessel by collateral vessels [14]. In addition, both post-PCI thrombolysis in myocardial infarction (TIMI) flow grade in IRA and post-PCI TIMI myocardial perfusion grade (MPG) were assessed. After grading collateralization, patients who had Rentrop ≤ 1 were defined as those with poorly developed collateral (PDC) group and patients who had Rentrop ≥ 2 defined as well developed collateral (WDC) group.

Pre-infarct angina was defined as at least one episode of typical transient (< 30 min) chest pain (Canadian Cardiovascular Society ≥ 1), in the preceding 24 h of index event. All patients were carefully assessed for pre-infarct angina. Coronary artery disease extension was calculated with Sullivan score, as described previously [15].

The general health status and functional capacity of the participants were assessed after the primary PCI. The patients on vitamin D or calcium supplementation, or with hyperparathyroidism or hypercalcemia, the patients with prior bone fracture or any musculoskeletal system disorder, previous coronary interventional procedures (by-pass graft surgery or PCI), oncological and hematological disorders, severe renal or hepatic failure, asthma, chronic and active inflammatory diseases, patients who showed TIMI flow grade > 1 at first contrast injection in the IRA, and patients admitted later than 12 h after chest pain onset were excluded from the study. Of 428 patients with acute STEMI enrolled in our study, 59 patients were excluded from the present analysis due to the following reasons: 21 patients with TIMI > 1 flow in the IRA at the first contrast injection, 12 patients admitted later than 12 h after chest pain onset, 5 patients with inadequate quality of angiographic image, 6 patients with coronary artery bypass grafting, 4 patients with severe renal failure, 3 patients with prior bone fracture, and 8 patients who were on vitamin D or calcium supplementation.

The institutional Ethics Committee approved the study, and each participant provided their written informed consent.

Laboratory analysis

Laboratory analyses include routine complete blood count, biochemistry, para-thyroid hormone, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitive C-reactive protein (hs-CRP) levels. Study procedure allowed us to measure the 25(OH)D3 levels before primary PCI application. Centrifuge used to separate serum and plasma, and materials were stored at –80°C until the test time. Serum 25(OH)D3 levels were measured by using a direct competitive chemiluminescent immunoassay (Elecsys; Roche Diagnostics, Maanheim, Germany). The detection threshold for 25(OH)D3 was 3 ng/mL. The intra-assay and inter-assay coefficient of variation were 4% and 7%, respectively.

The study was performed in Adana, Turkey, whose location is of a Mediterranean climate, with hot humid summers and soft climate in winters. Rainfall occurs during spring and autumn. The average temperatures of 40°C in summer and 8°C in winter were recorded.

Statistical analysis

Baseline, clinical and laboratory features of study patients were summarized as percentages

and frequencies for categorical variables and median values corresponding with 25th and 75th percentiles (Q25 and Q75) for continuous variables. The Kolmogorov-Smirnov test was used to identify the correctness of the distribution of continuous variables. Categorical variables were compared using the χ^2 test. Pearson and Spearman correlation coefficient was performed to examine the association between variables and AOCC. The effects of various variables on collateralization were calculated by using a univariate analysis. Variables showing an unadjusted $p < 0.10$ in logistic regression analysis were determined as risk markers. All significant parameters in the univariate analysis were selected in the multivariate model. Multivariate, stepwise backward conditional logistic regression analysis was used to obtain the independent predictors of collateralization. A receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of 25(OH)D3 to predict the presence of AOCC to IRA. Statistical analysis was performed by using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A two-tailed $p < 0.05$ was considered to be statistically significant.

Results

We included a total of 369 (75.1% male) acute STEMI patients with an average age of 57.7 ± 11.6 years. Poor developed (Rentrop grade 0 or 1) and well developed (Rentrop grade 2 or 3) collateralization was observed in 272 (73.7%) and 97 (26.3%) patients, respectively. The mean serum 25(OH)D3 level of study population was 16.9 ± 8.8 ng/mL, and 68.3% of patients had 25(OH)D3 levels below 20 ng/mL.

The WDC group was more likely to have better baseline characteristic risk including younger age (56 [49;64] vs. 58.5 [50;67]; $p = 0.034$), and freedom from prior diabetes (22.7% vs. 36.4%; $p = 0.016$), however hypertension (58.8% vs. 45.6%; $p = 0.033$) was higher when compared to the PDC group. The WDC group was also more likely to have presented with lower incidence of Killip class (at least two at admission), had higher left ventricular ejection fraction (LVEF), and lower in-hospital mortality rate (1% vs. 5.5%; $p = 0.047$). Other baseline and clinical features were similar between groups, which has been shown in Table 1.

Among the laboratory findings, 25(OH)D3 levels were significantly higher in WDC group as compared to PDC group (12 [10;18] ng/mL vs. 26 [21;32] ng/mL; $p < 0.001$). A box plot graphic of plasma 25(OH)D3 levels for comparison of poorly and well developed collateral groups was shown in Figure 1. A significant positive correlation was also found between plasma 25(OH)D3 levels and AOCC to IRA ($r = 0.577$, $p < 0.001$). However, hs-CRP ($r = –262$, $p < 0.001$), NT-proBNP ($r = –279$, $p < < 0.001$) and peak troponin T ($r = –105$, $p = 0.043$) levels demonstrated negative correlations with AOCC to IRA (Table 2).

At univariate analysis, age, diabetes mellitus, hypertension, LVEF, pre-infarction angina, Killip class, hs-CRP, NT-proBNP, peak troponin T, and 25(OH)D3 levels were obtained as determinants of AOCC to IRA. In multivariate analysis, 25(OH)D3 levels (odds ratio [OR] 1.246, 95% confidence interval [CI] 1.185–1.310, $p < 0.001$) together with hs-CRP (OR 0.840, 95% CI 0.746–0.945, $p = 0.004$), NT-proBNP (OR 0.998, 95% CI 0.998––0.999, $p = 0.001$), and peak troponin T (OR 1.000, 95% CI 1.000–1.000, $p = 0.004$) levels were found independent predictors of AOCC to IRA in patients with acute STEMI (Table 3). The cutoff value of admission plasma 25(OH)D3 level obtained by the ROC curve analysis was 10.5 ng/mL for prediction of AOCC to IRA (sensitivity: 96%, specificity: 67%). The area under the ROC curve (AUC) was 0.877 (95% CI 0.836–0.919, $p < 0.001$) (Fig. 2).

Discussion

The results of the present study have shown that in early hours of STEMI, collateralization grade to the IRA was independently associated with peak troponin T, NT-proBNP, hs-CRP, and admission plasma 25(OH)D3 levels.

The coronary collateral circulation is an important heart adaptation mechanism to prevent the ischemic myocardial injury, especially in the early hours of STEMI. After onset of acute STEMI, the incidence of AOCCs to IRA varies from 10% to 40% [3, 16]. In the present study, AOCC to IRA were found in 26.3% of patients within the first 12 h of acute STEMI onset. It has also been reported that patients with angiographically determined high grade collateralization to IRA had lower frequency of cardiogenic shock, better microvascular reperfusion, and smaller infarct size when compared to the other group [3–5]. Similarly, according to our results, these protective effects of AOCC on microvascular reperfusion, such as better post-PCI TIMI flow and post-PCI MBG, were more common in patients in WDC than PDC group. It is possible that AOCC to IRA due to high vitamin D level may lead to decreased microvascular injury and accelerated healing. We also observed higher

Table 1. Baseline and clinical characteristics of the study groups.

	PDC group (n = 272)	WDC group (n = 97)	P*
Age [years]	58.5 [50;67]	56 [49;64]	**0.034**
Gender, male	201 (73.9%)	76 (78.4%)	0.415
Body mass index [kg/m^2]	27.5 [24.6;29.4]	26.8 [24.1;29]	0.244
Hypertension	124 (45.6%)	57 (58.8%)	**0.033**
Diabetes mellitus	99 (36.4%)	22 (22.7%)	**0.016**
Smoking	156 (57.4%)	52 (53.6%)	0.552
Hyperlipidemia	46 (16.9%)	20 (20.6%)	0.441
Pre-infarction angina	53 (19.5%)	29 (30.2%)	**0.033**
Chest pain duration [h]	3.5 [2;5]	3 [2;5]	0.634
Previous myocardial infarction	45 (16.5%)	18 (18.8%)	0.638
Killip class ≥ 2	40 (14.7%)	6 (6.2%)	**0.031**
Left ventricular ejection fraction [%]	47 [38.6;52]	48 [42.1;52]	**0.003**
Culprit artery, LAD	139 (51.1%)	56 (57.7%)	0.287
Post-PCI TIMI ≥ 2	236 (86.7%)	92 (94.8%)	**0.037**
Post-PCI MBG > 2	55 (20.2%)	32 (33%)	**0.017**
Sullivan score	35 [30;50]	35 [27.5;40]	0.064
Rentrop score:			
0	124 (33.6%)		
1	148 (40.1%)		
2		74 (20.1%)	
3		23 (6.2%)	
In-hospital mortality	15 (5.5%)	1 (1%)	**0.047**

*t-test for independent samples and Pearson χ^2 test; data n (%) for categorical variables, median [interquartile range] for continuous variables; significant p values ($p < 0.05$) were indicated in boldface. LAD — left anterior descending artery; MBG — myocardial blush grade; PDC — poorly developed collateral; PCI — percuteneous coronary intervention; TIMI — thrombolysis in myocardial infarction; WDC — well developed collateral

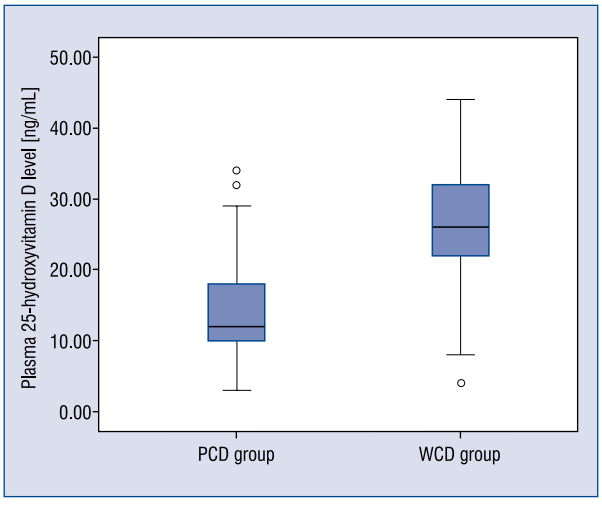

Figure 1. Box plot graphic of plasma 25-hydroxyvitamin D levels in patients with poorly developed collateral (PDC) group and well developed collateral (WDC) group (12 [10;18] ng/mL vs. 26 [21;32] ng/mL; $p < 0.001$).

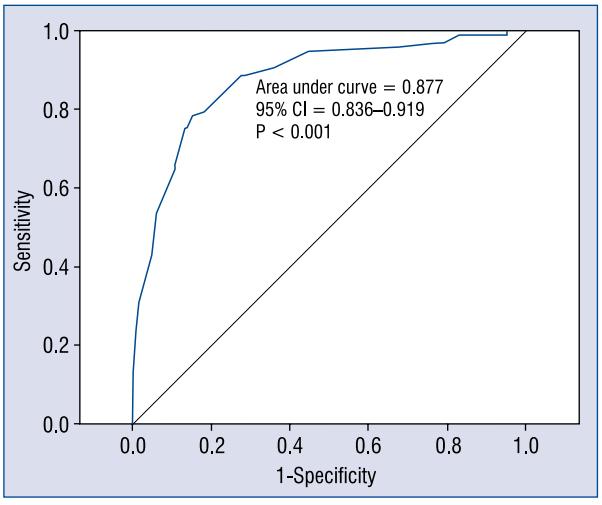

Figure 2. The receiver operating characteristic curve for 25-hydroxyvitamin D level for predicting development of acute occurring of collaterals to infarct related artery; CI — confidence interval.

Table 2. Laboratory findings of the study groups.

Variables	PDC group (n = 272)	WDC group (n = 97)	P*
WBC count [×1000/μL]	11.4 [9.4;14]	12.6 [10;15.1]	0.149
Hemoglobin [mg/dL]	13.6 [11.8;14.4]	14 [12;15.1]	0.159
Creatinine [mg/dL]	0.8 [0.7; 1.0]	0.8 [0.7; 0.9]	0.595
Total cholesterol [mg/dL]	187 [165;214]	188 [163;208]	0.696
Triglyceride [mg/dL]	92 [64;174]	102 [76;155]	0.541
HDL-C [mg/dL]	39 [33;45]	38 [32;45]	0.336
LDL-C [mg/dL]	132 [111;154]	129 [109;148]	0.695
hs-CRP [mg/L]	5.2 [3.2;7.2]	3.2 [2.4;5.2]	**< 0.001**
Peak troponin T [ng/mL]	1571 [574;3676]	1420 [666;2116]	**0.004**
NT-proBNP [pg/mL]	548 [161;1024]	234 [71;648]	**< 0.001**
Calcium [mg/dL]	9.1 [8.8;9.6]	9.3 [8.6;9.7]	0.853
Parathyroid hormone	52.4 [35;78]	53.9 [36.1;78]	0.626
25-hydroxyvitamin D [ng/mL]	12 [10;18]	26 [21;32]	**< 0.001**

*t-test for independent samples, data are median [interquartile range]; significant p values ($p < 0.05$) were indicated in boldface. HDL-C — high-density lipoprotein cholesterol; hs-CRP — high sensitive C reactive protein; LDL-C — low-density lipoprotein cholesterol; NT-proBNP — N terminal pro-B-type natriuretic peptide; PDC — well developed collateral; WBC — white blood cell; WDC — well developed collateral

Table 3. Significant predictors of acute occurring of collaterals to infarct related artery in univariable and multivariable logistic regression analyses.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	0.979	0.959–0.998	**0.035**			
Hypertension	0.588	0.368–0.940	**0.027**			
Diabetes mellitus	0.513	0.300–0.876	**0.014**			
Killip class ≥ 2	0.382	0.157–0.933	**0.035**			
Pre-infarction angina	1.789	1.054–3.035	**0.031**			
Ejection fraction	1.042	1.013–1.072	**0.004**			
Sullivan score	0.984	0.965–1.002	**0.080**			
Hs-CRP	0.813	0.738–0.894	**< 0.001**	0.840	0.746–0.945	**< 0.004**
Peak troponin T	1.000	1.000–1000	**0.011**	1.000	1.000–1000	**0.004**
NT-proBNP	0.998	0.998–0.999	**< 0.001**	0.998	0.998–0.999	**0.001**
25-hydroxyvitamin D	1.236	1.182–1.293	**< 0.001**	1.246	1.185–1.310	**< 0.001**

Significant p values ($p < 0.05$) were indicated in boldface. CI — confidence interval; Hs-CRP — high sensitive C-reactive protein; NT-proBNP — N terminal pro-B-type natriuretic peptide; OR — odds ratio

values of NT-proBNP, and troponin T levels together with higher incidence of Killip level ≥ 2, and mortality rate in PDC group when compared with WDC group.

It should be emphasized that we observed median level for 25(OH)D3 being 26 [21;32] ng/mL in WDC group, which was suboptimal and very close to optimal level (30–50 ng/mL) [17]. On the other hand, PDC group was definitely vitamin D-deficient with median 12 [10;18] ng/mL. Therefore, we may speculate that vitamin D has an important role in collateral development in the acute setting of STEMI. Angiogenesis and arteriogenesis are two mechanisms for developing collateral circulation as a response to myocardial ischemia [18]. Angiogenesis is a highly coordinated process and means formation of new capillary blood vessel from pre-existing blood vessel which requires interaction between endothelium, extracellular matrix, and surrounding cells mediated by growth

factors such as vascular endothelial growth factor (VEGF) [19]. The VEGF is one of these growth factors and improves impaired endothelium dependent relaxation of collaterals by nitric oxide (NO) mediated mechanism which is an important regulator of collateral growth [20, 21]. The VEGF mRNA and its ligand expression can occur within minutes due to myocardial ischemia [19, 22]. In a previous report, Ni et al. [23] demonstrated that blocking vitamin D receptors in mice caused a reduction in endothelial NO synthesis expression and endothelial function. Although it has been shown that vitamin D plays a key role in NO modulation in endothelial regeneration by stimulating VEGF and increasing the circulating endothelial progenitor cells (EPCs) [24, 25].

The stromal cell-derived factor 1 (SDF-1) and its ligand CXCR4 is another axis to promote angiogenesis. The homing of EPCs to the site of vascular injury depends on CXCR4 receptors [25, 26]. The injured vascular site and 25(OH)D3 stimulation have to be required together for synthesis and release SDF-1 from the injured tissue cells, which then mediate chemotatic stimulus to EPCs. 25(OH)D3 also increases the level of SDF-1 at the site of injured tissue by stimulating EPCs [25, 26].

Arteriogenesis is an alternative mechanism for collateral remodeling, mediated by change in shear stress. The pressure gradient between interconnecting network increases the blood flow velocity and fluid shear stress leads to collateral development due to occlusion of coronary artery [27, 28]. Stimulus of increased shear stress is transmitted to endothelial nucleus and leads to expression of several genes, including NO synthase, VEGF, and monocyte chemoattractant protein 1 (MCP-1). MCP-1 is a potent arteriogenic peptide [29]. In addition to chemoattractive effect on monocyte, VEGF receptor pathways have crosstalk with SDF-1 receptor pathways. Thus, shear stress may contribute to increase in the collateral flow by SDF-1 mediated mechanism [30]. Taken together, angiogenesis and arteriogenesis are two mechanisms of vessel growth, and vitamin D may contribute in various pathways of these processes to collateral remodeling.

The progression of atherosclerotic process and its acute complications are strongly related with low grade inflammation. Hs-CRP, one of the biomarkers of this inflammation, predicts cardiovascular risk [31]. Endothelial dysfunction seems to be a possible mechanism for explaining the role of hs-CRP in AOCCs to IRA. Previously it had been shown that increased levels of hs-CRP resulted in decreased expression of NO synthase, prostacyclin, up-regulation of endothelial adhesion molecules, and increased levels of superoxide radicals in vascular bed [32, 33]. Early after onset of ischemia, NO synthase activity increases and plays an important role in arteriogenesis by NO dependent vasodilatation of coronary collaterals [34]. Likewise, in our study, that inverse relationship between NO and hs-CRP contributes to the mechanism of inadequate AOCC to IRA.

Finally, we found that diabetes mellitus was associated with poor collateral development towards IRA in the acute setting of STEMI. Previous clinical and experimental studies have reported conflicting results about collateral development in diabetic or non-diabetic patients in the acute setting of myocardial infarction [35, 36]. It is well known that endothelial dysfunction and decreased NO synthesis are main features of diabetes mellitus. In addition, Mieno et al. [37] reported that diabetic patients have decreased EPC proliferation due to impaired VEGF stimulation. Accordingly, diabetic patients are more likely to have poor collateral development because of these underlying mechanisms in collateral development. However, several studies demonstrated better coronary collaterals in diabetic groups than in non-diabetics [35, 38]. The genetic factors could be a possible explanation and may interact with diabetes to improve the collateralization grade to IRA. Lin et al. [35] demonstrated that VEGF polymorphism in diabetic patients with the VEGF +405 C>G polymorphism had better collaterals than those without it. Another possible explanation could be that the experience of the first cardiac event of diabetic patients may occur at an advanced stage of atherosclerosis which is a critical predictor of collateral presence, as demonstrated by Niccoli et al. [38]. Even though, we found similar coronary extension score calculated by Sullivan scoring system [15] between the two groups. In this regard, we may conclude that this is the reason why the presence of previous acute myocardial infarction or advanced coronary atherosclerosis was not different between the two groups.

Limitations of the study

Our study has some limitations to be mentioned. Firstly, the diameter of collateral vessels under 100 μm could not be observed due to angiographic limitations. We also did not use indirect methods to better quantify the collateral flow, such as myocardial contrast-echocardiography of pressure-derived collateral flow index. In addition,

the results provided here cannot be generalized to all patients due to the fact that this is a single center study and our population included only one geographical region. Due to the nature of cross-sectional studies, our study could not support a causal relationship and requires confirmation in further well designed clinical trials. It is also important to remember that vitamin D status can change with various factors, such as season, geography, latitude, and sunlight exposure.

Conclusions

In conclusion, coronary collateral circulation is a complex process stimulated and mediated by various endogenous mediators including VEGF, SDF-1, MCP-1, NO, inflammatory markers, and neurohumoral markers. In addition to cardiac risk biomarkers, such as troponin T, NT-proBNP, or hs-CRP, our study also found that admission plasma 25(OH)D3 levels were associated with AOCC to IRA in acute STEMI patients. Therefore, vitamin D may be an important required hormone in interaction of various vascular regenerative pathways for collateral development in patients with acute STEMI. Its close relationship with AOCC may be a reasonable cause of poor prognosis in STEMI patients with vitamin D deficiency.

Conflict of interest: None declared

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