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Original article

Is there any link between vitamin D and coronary no-reflow phenomenon?

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Summary. Coronary no-reflow phenomenon (CNP) is associated with an increased risk of major cardiovascular adverse events. Vitamin D is closely associated with hypertension, stroke, myocardial infarction, cardiovascular adverse events, and endothelial dysfunction. Considering endothelial dysfunction is one of the main responsible factors of CNP. We aim to evaluate the association between vitamin D and CNP. The study group consisted of 109 patients. Taking into consideration the inclusion criteria, 60 patients with CNP and 49 patients without CNP were included in the study. CNP defined as TIMI grade <3 at the end of the procedure in the absence of any coronary dissection/spasm and/or less than 70% ST resolution at first hour ECG. Prevalence of CNP was found 55% in this study group. On univariate analysis age, balloon predilatation, stent diameter, serum creatinine, vitamin D, CRP level, initial TIMI flow <2, and reperfusion time >3 h were associated with CNP. On multivariate analysis reperfusion time >3 h, initial TIMI flow <2, and serum creatinine level were the independent predictors for CNP (OR 5.182; 95% CI: 3.159-8.327; p<0.001, OR 4.061; 95% CI: 2.729-6.327; p<0.001, OR 3.301; 95% CI: 1.937-4.623; p<0.001; respectively). In our study, we have found that reperfusion time >3 h, initial TIMI flow <2, and serum creatinine level were an independent predictor for CNP. Vitamin D was not found to be an independent predictor of CNP.

Key words: vitamin D, ST-elevation myocardial infarction, no-reflow phenomenon

Background

Despite the medical and technological improvements of the revascularization procedures in coronary artery diseases, ST-elevation myocardial infarction (STEMI) remains a significant health concern. The primary percutaneous coronary intervention (pPCI) is a favourable treatment option for restoring perfusion to the affected area of the myocardium as soon as possible. Coronary no-reflow phenomenon (CNP) was defined as Thrombolysis in myocardial infarction (TIMI) flow grade <3 after vessel recanalisation despite the absence of angiographic stenosis, spasm, dissection, or thrombosis after pPCI. CNP occurs in 11-41% of STEMI patients treated by primary pPCI and is associated with the poor left ventricular function, arrhythmias, poor in-hospital and one-year survival (1).

The mechanism of CNP is complex and not fully understood. Possible mechanisms of CNP were microthromboemboli, irreversible cardiomyocyte and endothelial damage/dysfunction caused by ischemia, activation of reactive oxygen species, endothelial cell necrosis leads to the destruction of tight and adherens junction and loss of vascular integrity (2). Myocardial contrast echocardiography, magnetic resonance imaging (MRI), myocardial blush grade, intracoronary pressure measurements, intracoronary Doppler, Virtual histology intravascular ultrasound were a useful

diagnostic tool for CNP. A rapid resolution of ST-segment elevation is highly suggestive of reperfusion. ST-segment resolution <70% at 60 min is a descriptive marker of CNP (1, 3).

Vitamin D is a fat-soluble steroid responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects. Vitamin D receptors are expressed in a variety of tissues, including cardiomyocytes, vascular smooth muscle cells, and endothelial cells. Vitamin D deficiency contributes to the development of cardiovascular diseases through its association with risk factors, such as diabetes mellitus (DM), hypertension (HT), and atherosclerosis and also through events such as myocardial infarction, stroke, and congestive heart failure. Also, vitamin D has anti-inflammatory effects and prevents cholesterol removal by macrophages and foam cells formation on vessel walls. Vitamin D deficiency causes endothelial dysfunction through its direct or indirect association through the up-regulation of the renin-angiotensin system or via induction of smooth muscle proliferation and a pro-inflammatory state (4-9). Sugden et al. (10) demonstrated that decreased serum vitamin D level was associated with decreased flow-mediated dilatation, and vitamin D supplementation can improve endothelial dysfunction in patients with DM.

In this context, we aim to evaluate the association between serum vitamin D level and CNP in patients underwent pPCI.

Methods

The study group consisted of 124 consecutive patients, who underwent primer PCI due to first acute STEMI were evaluated prospectively. Among them, 15 patients were excluded from the study because of not undergoing pPCI, cardiogenic shock, symptom to balloon time more than 12 hours, history of coronary artery disease (previous coronary artery bypass graft surgery or PCI), and not achieving coronary artery patency.

The diagnosis of acute STEMI was established using The Joint European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association definition of STEMI.(11) All patients received aspirin (300 mg) and clopidogrel (600 mg) prior to their transfer to the catheterisation laboratory. Emergency coronary angiography was performed using the percutaneous femoral or radial approach. Heparin (100 U/kg) was administered in all patients during pPCI procedure. Occlusion of the infarct-related coronary artery was crossed using various guide wires, and predilatation was performed via balloon angioplasty if necessary. Routine stenting was attempted directly or following balloon angioplasty. The drug-eluting stent was implanted at the site of the ruptured atherosclerotic plaque. 12-lead ECG was obtained 60 minutes after successful pPCI. All of the patients were treated according to the recommendations of the latest ESC Guidelines for the Management of Patients with STEMI (12). The usage of thrombus aspiration catheter and administration of glycoprotein IIb/IIIa inhibitors were chosen according to the interventional cardiologist's decision.

Epicardial coronary blood flow was quantified visually using the Thrombolysis in Myocardial infarction (TIMI) flow grade classification (13). Initial TIMI flow was assessed at the beginning of the procedure prior to wire insertion, and final TIMI flow was assessed at the end of the procedure. No-reflow was defined as TIMI grade <3 at the end of the procedure in the absence of any coronary dissection or spasm. The TIMI flow grades were evaluated by 2 blind cardiologists. The frame rate of cine images were 30 frames per seconds.

ST-segment elevation in mm was measured 20 ms after the J point. The sum of ST-segment elevations was calculated for all leads. A percentage ST-segment resolution <70% was accepted as an ECG sign of the No-reflow. Electrocardiograms were evaluated in a blinded manual manner by two experienced cardiologists. CNP was described as TIMI flow <3 after pPCI and/or <70% ST-segment resolution at 60 minute ECG in our study.

Peripheral venous blood samples were obtained from all patients and controls. Each blood sample was left to coagulate for 30 minutes, and then centrifuged at 2000 g. for 15 minutes to separate serum. Serum aliquots were immediately labeled and stored at -20°C until analysis.

Serum 25-OH Vitamin D level was analyzed using commercial reagents by the Chemiluminescent Microparticle Immunoassay method on Abbott

Architect i2000SR (Abbott Laboratory Abott park, Chicago, IL, USA). The method of measurement was carried out according to the manufacturer instructions.

The data of patients were analysed for the demographic features, echocardiographic parameters including ejection fraction, biochemical parameters, and coronary angiography.

Echocardiographic examination

Transthoracic echocardiography was performed within 48 hours of admission using a Vivid S5 (GE healthcare) echocardiography device and Mass S5 probe (2-4 MHz). Standard two-dimensional and colour flow Doppler views were acquired according to the guidelines of American Society of Echocardiography and European Society of Echocardiography (14). The ejection fraction was measured according to the Simpson's method.

Patients with DM were identified on admission as those with documented DM using either oral hypoglycemic agents or insulin treatment. Hyperlipidemia (HL) was defined as total cholesterol at least 200 mg/dL or using antihyperlipidemic therapy on admission. HT was defined as blood pressure above 140/90 mmHg or using antihypertensive therapy on admission.

Statistical analysis

Statistical analysis was performed using the SPSS (version 20.0, SPSS Inc., Chicago, Illinois) software package. Continuous variables were expressed as the mean±standard deviation (mean± SD), and categorical variables were expressed as a percentage (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student's t-test was used to evaluate continuous variables showing normal distribution, and Mann-Whitney U-test was used to evaluate variables that did not show normal distribution. A p-value <0.05 was considered statistically significant. To identify predictors of CNP, the following variables were initially assessed in a univariate model: age, reperfusion time >3h, initial TIMI flow <2, stent diameter, balloon predilatation, serum creatinine, vitamin D, and CRP. Significant variables in univariate analysis were then entered into a multivariate logistic-regression analysis using backward stepwise selection.

Results

Prevalance of CNP was found 55% in this study group. The demographic characteristics of both group are summarized in Table 1. There was no significant difference between both groups regarding female gender, HT, current smoking, HL, and Body mass index (69.4% vs. 68.3% p=0.906, 32.6% vs. 33.3% p=0.738, 53.1% vs 58.3% p=0.304, 20.4% vs 25% p=0.322, 28.3 vs 30.1 kg/m^2 p=0.437; respectively) (Table 1). There was significant diffrence between both groups regarding age and DM (59.4±10.7 vs. 64.1±10.1 years p=0,022, 34.6% vs. 48.3% p<0.001; respectively) (Table 1).

There was no significant difference between both groups regarding biochemical parameters such as white blood cell, haemoglobin, and urea (11.5±3.5 vs 12.1±2.8 10^3/µL p=0.291, 13.8±1.9 vs 14.3±1.2 g/dl p=0.065, 39.1±16.2 vs 37.3±7.3 mg/dl p=0.494; respectively) (Table 2). There were significant diffrence between both groups regarding reperfusion time >3h, balloon predilatation, stent diameter, initial TMI flow <2, serum vitamin D, C reactive protein (CRP), creatinine level (16.3% vs 45% p<0.001, 53.1% vs 71.7% p=0.045, 3.05±0.41 vs 2.85±0.34 mm p=0.008, 46.9% vs 71.6% p<0.001, 19.3±6.9 vs 13.2±8.5 ng/ml p<0.001, 1.6±2.1 vs 2.4±2.2 mg/dl p:0.041, 0.81±0.17 vs 0.88±0.12 mg/dl p=0.007; respectively) (Table 2).

On univariate analysis age, serum creatinine, vitamin D, CRP, balloon predilatation, stent diameter,

Table 1. General characteristics of patients

Patient characteristics	Coronary no-reflow phenomenon		p
	- (49)	+ (60)	
Age (years)	59.4±10.7	64.1±10.1	**0.022**
Female Gender, n(%)	34 (69.4)	41 (68.3)	0.906
Hypertension, n(%)	16 (32.6)	20 (33.3)	0.738
Diabetes Mellitus, n(%)	17 (34.6)	29 (48.3)	**0.02**
Current Smoking, n(%)	26 (53.1)	35 (58.3)	0.304
Hyperlipidemia, n(%)	10 (20.4)	15 (25)	0.322
Body Mass Index, (kg/m^2)	28.3 (22.1±35.7)	30.1 (24.6±36.9)	0.437

Table 2. Laboratory, echocardiographic, and angiographic parameters

Variables	Coronary no-reflow phenomenon		p
	- (49)	+ (60)	
White Blood Cell (10^3/μL)	11.5±3.5	12.1±2.8	0.291
Haemoglobin (g/dl)	13.8±1.9	14.3±1.2	0.065
Urea (mg/dl)	39.1±16.2	37.3±7.3	0.494
Creatinine (mg/dl)	0.81±0.17	0.88±0.12	**0.007**
C reactive protein (mg/dl)	1.6±1.1	2.4±2.2	**0.041**
Vitamin D (ng/ml)	19.3±6.9	13.2±8.5	**<0.001**
Ejection Fraction (%)	37.9±10.3	35.4±9.7	0.549
Initial TIMI flow <2 (n,%)	23 (46.9)	43 (71.6)	**<0.001**
Stent Diameter (mm)	3.05±0.41	2.85±0.34	**0.008**
Stent Length (mm)	20.7±7.1	22.7±5.5	0.055
Balloon Predilatation (n,%)	26 (53.1)	43 (71.7)	**0.045**
Reperfusion Time >3 h, (n,%)	8 (16.3)	27 (45)	**<0.001**

Table 3. Univariate analysis of predictors for coronary no-reflow phenomenon

Predictor variables	OR (95% C.I.)	p
Age (years)	2.681 (1.376-4.327)	**<0.001**
Serum Creatinine (mg/dl)	3.153 (1.839-4.638)	**<0.001**
Serum Vitamin D (ng/ml)	2.147 (1.373-3.427)	**<0.001**
Serum C Reactive Protein (mg/dl)	2.549 (1.937-3.581)	**0.01**
Balloon dilatation (n,%)	1.951 (1.327-2.638)	**0.001**
Stent Diameter (mm)	3.926 (2.379-5.734)	**<0.001**
Reperfusion Time >3 h (n,%)	4.269 (2.837-6.823)	**<0.001**
Initial TIMI Flow <2 (n,%)	3.929 (2.837-7.634)	**<0.001**

reperfusion time >3h, and initial TIMI flow <2 were associated with CNP (OR 2.681; 95% CI: 1.376-4.327; p<0.001, OR 3.153; 95% CI: 1.839-4.638; p<0.001, OR 2.147; 95% CI: 1.373-3.427; p<0.001, OR 2.549; 95% CI: 1.937-3.581; p=0.01, OR 1.951; 95% CI: 1.327–2.638; p=0.001, OR 3.926; 95% CI: 2.379-5.734; p<0.001, OR 4.269; 95% CI: 2.837-6.823; p<0.001, OR 3.929; 95% CI: 2.837-7.634; p<0.001; respectively) ((Table 3).

Table 4. Multivariate analysis of predictors for coronary no-reflow phenomenon

Predictor variables	OR (95% C.I.)	p
Serum creatinine (mg/dl)	3.301 (1.937-4.623)	**<0.001**
Reperfusion time >3 h (n,%)	5.182 (3.519-8.359)	**<0.001**
Initial TIMI flow <2 (n,%)	4.061 (2.729-6.327)	**<0.001**

On multivariate analysis serum creatinine level, reperfusion time >3 h, and initial TIMI flow<2 were independent predictors for CNP (OR 3.301; 95% CI: 1.937-4.623; p<0.001, OR 5.182; 95% CI: 3.519-8.359; p<0.001, OR 4.061; 95% CI: 2.729-6.327; p<0.001; respectively) (Table 4).

Discussion

In our study, we have found that serum creatinine level, reperfusion time >3 h, and initial TIMI flow <2 were an independent predictor for CNP. Vitamin D was not found to be an independent predictor of CNP.

In previous studies, CNP occurs in 11-41% of STEMI patients treated by pPCI (1). In our study, the prevalence of CNP was 55%. Our higher prevalence of CNP was associated with our definition of CNP. In our study, CNP was described as <70% ST-segment resolution at 60 minute ECG and/or TIMI flow <3 after pPCI. Although the most of the studies used TIMI flow method for assessing CNP TIMI flow method is less accurate than myocardial blush grade and MRI. Therefore, not only TIMI flow grade but also ECG criteria of CNP (<70% STR) were used to evaluate of CNP in our study. Our higher ratio of CNP might be associated with definition criteria of CNP.

The pathophysiology of CNP is still not fully understood. Possible etiological factors of CNP are pre-existing microvascular dysfunction, distal microthrombo-embolization due to high platelet activity, increased thrombus burden, ischemic injury, reperfusion injury, swelling of myocardial cells compressing microvascular vessels, and individual susceptibility. Endothelial dysfunction is one of the major mechanisms leading to CNP, as we found in our results that high creatinine levels in patients with CNP were signifi-

cantly increased. The reduction in renal function has been proven to cause retention of vasotoxic substances and cause metabolic changes that lead to increase reactive oxygen species. These changes are believed to have an important role in creating an atherogenic milieu. As a result, the plasma concentration of endothelium-derived protein will be increased, and endothelium-dependent vasodilatation will be decreased. The changes of this level are responsible for increasing soluble vascular cell adhesion molecule-1 expression, the earlier step of endothelial dysfunction (15). In our study, we found that serum creatinine level was independently associated with CNP.

It is well known that prolonged ischemia was associated with distal capillary oedema, swelling of myocardial cells, neutrophil plugging and alterations of capillary integrity (16). Additionally, delayed reperfusion can result in more organised intracoronary thrombus which might increase the risk of distal embolisation (17). The thrombus is rich in thrombocytes in the early phase of STEMI, with a longer time to reperfusion, the thrombus takes on more erythrocytes and becomes more firm. Prolonged ischemia may disrupt the microvascular bed, and the degree of this disruption is known to be a key component in the pathogenesis of CNP (18). Delayed reperfusion leads to the greater destruction of the microvasculature, which is why an increased rate of no-reflow is seen in cases of prolonged reperfusion. Animal studies showed that longer duration of occlusion of the coronary artery is associated with CNP after reopening the artery (19). Jawad et al. (20)reported that that delayed presentation >6 h from symptom onset to be independently associated with CNP. In accordance with previous studies (18-20), we found that prolonged revascularisation (reperfusion time >3 h) was an independent predictor of CNP.

Several studies showed that initial TIMI flow was independently associated with CNP (20, 21). Brodie et al. (22) reported that procedural success rate was better in patients with initial TIMI 2-3 flow. Additionally, De Luca et al. (23) showed that initial good TIMI flow was strongly associated with post-procedural TIMI 3 flow and myocardial blush grade 2-3. Good patency of the infarct-related artery prior to PCI associated with lower thrombus burden, spontaneous endogenous lysis of the thrombus, resolution of vasospasm, and smaller infarct size. In accordance with previous studies (20-23), in our study, we found that initial TIMI flow grade was an independent predictor of CNP.

Growing evidence demonstrated that there was a strong association between vitamin D and cardiovascular disease. Vitamin D deficiency causes endothelial dysfunction through its direct or indirect association through the up-regulation of the renin-angiotensin system or via induction of smooth muscle proliferation and a pro-inflammatory state (4-9). Several studies demonstrated that vitamin D deficiency was associated with decreased flow-mediated dilatation, and vitamin D supplementation can improve endothelial dysfunction in various study population such as healthy subjects, DM, stroke, obesity, rheumatoid arthritis, and systemic lupus erythematosus (24, 25). Considering that endothelial dysfinction is one of the possible mechanism of CNP, we conducted this study. In our study, we found that vitamin D was not an independent predictor of CNP.

Our study has some limitations. First, small sample size. Second, we didn't use intravascular USG to quantify evaluate thrombus burden and plaque content. Third, we didn't perform the myocardial blush grade. Fourth, we didn't evaluate serum calcium and parathyroid hormone level.

Conclusion

In our study, we have found that serum creatinine level, reperfusion time >3 h, and initial TIMI flow <2 were an independent predictor for CNP. Vitamin D was not found to be an independent predictor of CNP. Although endothelial dysfunction is one of the possible mechanism of the CNP, other important pathophysiological mechanisms including microthromboemboli, irreversible cardiomyocyte and endothelial damage/dysfunction caused by ischemia, activation of reactive oxygen species, endothelial cell necrosis might outweigh rather than endothelial dysfunction. Further studies are needed to evaluate the association between CNP and vitamin D.

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