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CLINICAL STUDY

Evaluation of the inflammatory parameters for predicting stent thrombosis

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ABSTRACT

OBJECTIVES: Recent research demonstrated that classic inflammatory mediators were responsible for the development of stent thrombosis. We aimed to examine the relationship between predictors such as basophils, mean platelet volume (MPV), and vitamin D, which represented allergic, inflammatory, and anti-inflammatory states, and stent thrombosis after percutaneous coronary intervention.

METHODS: In this observational case-control study, patients (n: 87) with ST-elevated myocardial infarction (STEMI) with stent thrombosis formed group 1, and (n = 90) with STEMI without stent thrombosis formed group 2. 25-OH vitamin-D and other laboratory values were obtained at the time of admission to the emergency room.

RESULTS: In comparison to group 2, MPV was higher in group 1(9.05±0.89 vs 8.17±1.37 fL, respectively; p=0.002). Group 2 had a higher basophil count than group 1(0.03±0.05 vs 0.07±0.080; p=0.001). In comparison to group 2, group 1 had a greater vitamin-D level (p=0.014). The MPV and basophil count were found as predictors for stent thrombosis in the multivariable logistic analyses. When MPV increased by one unit, the risk of stent thrombosis increased 1.69-times (95% CI: 1.038–3.023). Basophil counts below 0.02 increased the risk of stent thrombosis 12.74-times (95% CI: 4.22–36.00).

CONCLUSION: Increased MPV and basophil depletion might be predictors for coronary stent thrombosis following percutaneous coronary intervention *(Tab. 4, Fig. 2, Ref. 25)*. Text in PDF *www.elis.sk*

KEY WORDS: MPV; basophil; vitamin D; stent thrombosis.

Abbreviations: MPV – mean platelet volume, STEMI – ST-elevated myocardial infarction, ACS – Acute coronary syndrome, PCI – percutaneous coronary intervention, MACE – major adverse cardiovascular events, CRP – C-reactive protein, IL-6 – interleukin 6, TNF – tumor necrosis factor, EWM – excess winter mortality, DES – drug-eluting stents, BMS – bare metal stent

Introduction

Coronary stent thrombosis is defined as angiographic evidence of thrombus in a stent implanted previously. It is a serious clinical event with mortality rates of 20–40 %. There are three categories of risk factors for stent thrombosis: patient, procedure, and device related (1). A stented arterial wall's neointima is where an atherosclerotic plaque known as neoatherosclerosis develops. It has been reported to be the root of 43.3 % of thrombosis in stents (2). Traditional inflammatory cells such neutrophils, lymphocytes, and macrophages have been linked to the etiology of unstable coronary plaque. Recent research, however, raised the possibility that allergic inflammatory reactions might have a pathogenetic function. Basophils have been considered as circulating precursors of tissue mast cells. Activated mast cells develop peripheral basophil depletion. The prevalence of intraplaque hemorrhage and the amount of mast cells are associated. According to human pathologic research, plaque rupture or plaque erosion locations contained activated mast cells (3).

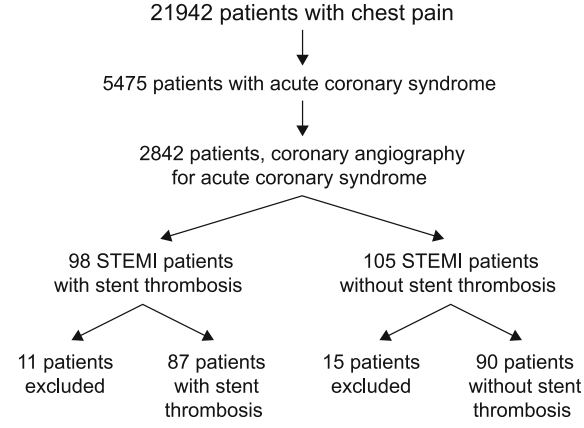

Fig. 1. Group 2 contained 90 patients with STEMI but no stent thrombosis.

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Tab. 1. Demographic characteristics of the groups.

		Group1 (n=87)	Group 2 (n=90)	p
Age (year)	Min–Max (Median)	38–79 (56)	38–85 (56)	a0.540
	Mean±Sd	58.94±10.37	57.35±11.47	
Sex; n (%)	Female	27 (31)	21 (23.3)	b0.249
	Male	60 (69)	69 (76.7)	
Diabetes; n (%)	No	58 (66.70)	52 (57.80)	b0.223
	Yes	29 (33.30)	38 (42.20)	
Hypertension; n (%)	No	25 (28.70)	62 (68.90)	b0.001**
	Yes	62 (71.30)	28 (31.10)	

aStudent t Test, bPearson Chi-Square Test, **p<0.01

Platelets play a role in either endothelial dysfunction or susceptible plaque rupture in atherosclerosis. Platelets interact with endothelial cells and this causes excessive platelet activation. Consequently, platelets have a shorter half time and increase in volume. Acute coronary syndrome's (ACS) thrombotic consequences and platelet activation are both strongly influenced by inflammation (4).

It is well known that vitamin D primarily affects the metabolism of calcium and bones (5). Many inflammatory responses are regulated at various levels by vitamin-D signaling (6). Numerous studies have demonstrated how vitamin D deficiency affects cardiovascular illness, particularly ischemic heart disease (5). In certain investigations, vitamin D deficiency was linked to myocardial infarction, cardiovascular mortality, and coronary artery disease (7–9). The presence of vitamin-D was found to be a predictive factor for subsequent myocardial infarction (8, 9). In addition, vitamin D deficiency increases the relative risk for myocardial infarction as much as 2.42-times (7). However, this area remains controversial with several studies questioning this association (10). Therefore, as the aim of present study, we researched the relationship between predictors such as basophil count and vitamin-D, which represent allergic and anti-inflammatory states, and coronary stent thrombosis after percutaneous coronary interventions.

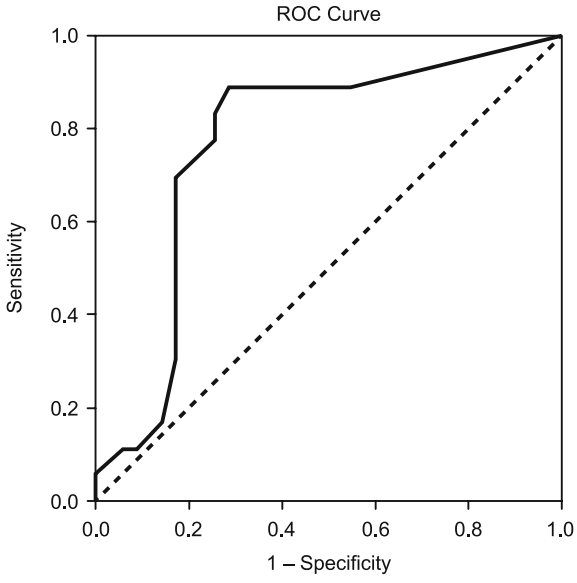

Fig. 2. The cut-off value for the basophil count was 0.02. When the basophil count decreased beyond that level, the risk of developing stent thrombosis increased as much as 13-fold.

Method

Between February 2014 and March 2016, 21,942 consecutive patients who presented with chest pain at Siyami Ersek Hospital cardiology clinic emergency service were analyzed. Academic Research Consortium criteria were used to determine definitive stent thrombosis (11). 87 individuals with stent thrombosis were included in group 1 of our cross-sectional study. Group 2 contained 90 patients with STEMI but no stent thrombosis (Fig. 1).

According to the American Diabetes Association criteria, a subject was considered to have diabetes mellitus if the patient was aware of the diagnosis. When a patient had chronic antihypertensive medication treatment, their arterial pressure was greater than 140/90 mmHg, or they had a prior diagnosis of hypertension.

The exclusion criteria were liver, kidney, or allergic disease; hyperparathyroidism; use of drugs including vitamin-D and calcium; and history of malignancy and inflammatory disease. Patients with acetylsalicylic acid or clopidogrel resistance, those with stent thrombosis within 24 hours after implantation, and those suspected of having edge dissection or mispositioning were all excluded from the study. The study protocol (HNEAH-KAEK 2020/265-3053) was approved by the regional ethics committee. All patients gave their informed consent.

The Judkins technique was used for the angiography of the patients in groups 1 and 2. According to the recommendations of the European Society of Cardiology, a coronary angiography was completed (12). Angiographic evidence of vessel occlusion at the site of previous stent implantation was considered as stent thrombosis. Clear stent live was used to visualization of the stent structure in all patients. Angiographic procedures were performed by expert invasive cardiologists (Siemens Axiom Artis Zee, Germany).

When patients were admitted to the emergency room, other laboratory values, including 25-OH vitamin D, were acquired from the patients (Coulter LH 780, Bechman Coulter Ireland).

Statistical analysis

The program used was Number Cruncher Statistical System NCSS 2007 (Kaysville, Utah, USA). To present the findings, mean, median, and standard deviation were employed. The normality of the data was examined using the Shapiro-Wilk test. ANOVA one-way and the Bonferroni correction were used to evaluate variables having a normal distribution. The Kruskal-Wallis test and the Bonferroni-Dunn test were applied if the normality test was unsuccessful. In order to compare categorical variables, the Pearson Chi-square ($\chi 2$) test was used. The risk variables for thrombosis in stents were identified using logistic regression analysis. The cut-off values for basophil counts were determined using receiver operating characteristics (ROC) analysis. Statistical significance was defined as a p less than 0.05.

Tab. 2. Laboratory characteristics of the groups.

		Group 1	Group 2	p
Fasting glucose mg/dL	Min–Max (Median) Mean±SD	80–329 (134) 141.45±51.37	77–288 (103.5) 121.27±50.88	c0.010**
Triglyceride mg/dL	Min–Max (Median) Mean±SD	54–927 (132) 170.40±147.06	56–561 (128) 160.81±113.29	c0.572
WBC x10^3/m^3	Min–Max (Median) Mean±SD	7.10–17.10 (9.5) 10.21±2.41	4.60–16.40 (9.30) 10.16±3.33	c0.644
Hemoglobin g/dL	Min–Max (Median) Mean±SD	8.40–16.30 (13.10) 13.25±1.72	7.30–17.10 (14.20) 13.73±1.89	c0.160
Calcium mg/dL	Min–Max (Median) Mean±SD	8–10.90 (9.40) 9.30±0.56	7.50–9.90 (8.70) 8.80±0.67	a0.001**
Phosphorous mg/dL	Min–Max (Median) Mean±SD	2.40–5.30 (3.40) 3.49±0.89	1.20–5.60 (2.60) 2.69±0.90	c0.011*
Uric acid mg/dL	Min–Max (Median) Mean±SD	4.40–8.40 (5.50) 5.84±1.14	2.60–10.50 (5.20) 5.69±1.87	a0.738
LDL mg/dL	Min–Max (Median) Mean±SD	56–216 (113) 117.14±34.43	43–164 (96) 100.29±35.36	a0.054
HDL mg/dL	Min–Max (Median) Mean±SD	23–67 (41) 39.91±8.82	16–63 (34) 35.29±9.69	a0.047*
Neutrophil 10^3/mm^3	Min–Max (Median) Mean±SD	1.70–13.80 (6.60) 7.26±2.56	3.60–30 (6.80) 8.19±4.96	c0.987
Lymphocyte 10^3/mm^3	Min–Max (Median) Mean±SD	0.70–4.10 (2) 2.09±0.79	0.2–4.5 (1.9) 1.92±0.99	c0.257
NLR	Min–Max (Median) Mean±SD	0.70–12 (3.20) 4.14±2.60	1.20–61.50 (3.80) 7.01±10.44	c0.411
CRP mg/dL	Min–Max (Median) Mean±SD	0–8.40 (0.80) 1.57±2.10	0–15.10 (0.40) 1.21±2.65	c0.241
MPV fL	Min–Max (Median) Mean±SD	7.40–11 (9) 9.05±0.89	6–12 (7.90) 8.17±1.37	a0.002**
Platelet 10^3/mm^3	Min–Max (Median) Mean±SD	124–496 (246) 255.09±80.94	81–387 (217,5) 222.31±63.05	a0.061
25 OH cholecalciferol ng/mL	Min–Max (Median) Mean±SD	6.30–29 (15.30) 15.59±4.96	5.40–23.90 (11.30) 12.47±5.13	a0.014*
Creatinine mg/dL	Min–Max (Median) Mean±SD	0.50–1.30 (0,8) 0.85±0.22	0.20–1.50 (0.80) 0.88±0.26	a0.606
EF %	Min–Max (Median) Mean±SD	35–60 (55) 52.79±6.87	20–65 (50) 50.56±9.55	c0.403
HbA1c %	Min–Max (Median) Mean±SD	2.40–8.20 (5.40) 5.27±2.09	5.30–9.70(6) 7.00±1.87	a0.041*
Monocyte 10^3/mm^3	Min–Max (Median) Mean±SD	0.20–2.40 (0.60) 0.69±0.42	0.30–1.60 (0.60) 0.65±0.26	c0.764
Basophil 10^3/mm^3	Min–Max (Median) Mean±SD	0–0.20 (0.01) 0.03±0.05	0–0.50 (0.06) 0.07±0.08	c0.001**
MPV/lymphocyte	Min–Max (Median) Mean±SD	2–13.10 (4.50) 5.19±2.72	1.80–33 (4.60) 6.18±5.87	c0.977
MPV/neutrophil	Min–Max (Median) Mean±SD	0.70–6.50 (1.30) 1.46±0.97	0.30–2.30 (1.30) 1,26±0,57	c0.497
Platelet/lymphocyte	Min–Max (Median) Mean±SD	54.40–354.30 (125.30) 140.26±70.74	48.5–1250 (117.2) 163.16±196.15	c0.823

aStudent t Test, cMann Whitney U Test, *p<0.05, **p<0.01 WBC: White blood cell. LDL: low-density lipoprotein cholesterol. HDL: high-density lipoprotein cholesterol. NLR: neutrophil to lymphocyte ratio. CRP: C-reactive protein. MPV: mean platelet volume. EF: ejection fraction. HbA1c: glycated hemoglobin.

Results

Tables 1 and 2 detail the research groups' clinical and demographic characteristics. In group 1, hypertension was more common (hypertension: group 1, n = 62; group 2, n = 28; p = 0.001). 34 patients experienced coronary stent thrombosis at an early stage. The remaining patients (n = 53) developed late stent thrombosis.

Monocyte, neutrophil, lymphocyte, and white blood cell counts were comparable between groups. Group 2 had greater basophil levels than Group 1 did (group 1, 0.03 ± 0.05; group 2, 0.07 ± 0.08; p = 0.001). Group 1 had a greater MPV than Group 2 (group 1, 9.05 ± 0.89 fL; group 2, 8.17 ± 1.37fL; p = 0.002). Group 1 had higher vitamin D levels than Group 2 (group 1, 15.59 ± 4.96 ng/mL; group 2, 12.47 ± 5.13 ng/mL; p = 0.014) (Tab. 2).

In Table 3, the multivariable logistic regression analysis predictors of stent thrombosis are shown. The chance of stent thrombosis in individuals with vitamin D deficiency was insignificant in this model. However, logistic regression analysis showed that the probability of stent thrombosis was raised by MPV levels and decreased basophil numbers. The risk of stent thrombosis rose up to 1.69-times when the MPV increased by one unit (95% CI: 1.038–3.023) (Tab. 4, Fig. 2). The risk of stent thrombosis increased up to 13-times with a basophil level below 0.02 (95% CI:4.22–36.01). MPV levels and basophil counts were shown to be independent risk factors for stent thrombosis.

Discussion

We set out to investigate the link between the combination of thrombotic state, allergic and inflammatory response, vitamin D, and coronary stent thrombosis.

The following were the key conclusions:

1. Thrombotic state: MPV was a standalone predictor of acute stent thrombosis development. When MPV surpasses 10.55 fL in angina patients, the risk of acute coronary syndrome rises 5.08 times (13). Additionally, individuals receiving emergency percutaneous coronary intervention (PCI) had greater MPV levels than those undergoing elective PCI (14). Patients who experienced major adverse cardiovascular events (MACE) after PCI had high MPV and neutrophil leukocyte ratio levels for up to 29 months. There were just 26 MACE patients in that research (15). A distinct predictor of a poor response to dual antiplatelet medication is the size of the platelet, which is more frequently reticulated than smaller platelets and contains more prothrombotic material (16).

Tab. 3. Predictors of stent thrombosis in logistic regression analysis (between group 1 and group 2 (n = 177)).

	p	ODDS	95% CI	
			Lower	Upper
Sex (female)	0.167	0.169	0.014	2.096
CRP	0.760	0.925	0.559	1.530
MPV	0.041*	1.694	1.038	3.023
25 OH cholecalciferol	0.315	1.098	0.915	1.317
Basophil (≤0.02)	<0.001**	12.739	4.220	36.007
Fasting blood sugar	0.137	1.009	0.997	1.022
Platelet	0.901	1.001	0.985	1.017

*p<0.05

Tab. 4. The cut-off relationship between groups and basophil count.

		Group 2		Group1		p
		n	%	n	%	
Basophil count	**> 0.02**	76	86.40	30	34.50	[b]**0.001****
	≤ 0.02	12	13.60	57	65.50	

[b]Pearson Chi-square Test, **p<0.01

In our study, when stent thrombosis occurred, 94 % of patients were taking dual antiplatelet therapy. Balli et al showed the cut-off value of MPV that detected acute stent thrombosis was > 9.1 fL in patients with acute coronary syndrome (17). Their findings support our study; however, our methodology was different from theirs. In our study, as the MPV increased by one unit, the risk of stent thrombosis increased as much as 1.69-times. In a prospective cohort study from Karachi, MPV levels exceeding 11.25 fL had increased myocardial infarction risk following acute coronary syndrome (18).

2. Vitamin D and the traditional inflammatory state: In our investigation, inflammation had no impact on the onset of stent thrombosis. Slightly increased C-reactive protein (CRP) levels did not predict acute coronary stent thrombosis when inflammatory markers in STEMI patients with stent thrombosis were compared to STEMI patients without stent thrombosis. According to Cure et al., patients with 25-OH vitamin-D ≤ 20 ng/mL have higher cardiac mortality and morbidity when their MPV levels are high. They hypothesized that lower levels of vitamin D raised cytokine levels, including those of interleukin (IL-6) and tumor necrosis factor (TNF)-alpha, and that higher levels of cytokine exacerbated oxidative stress and platelet activation (19). The vitamin-D levels of the patients in our study were likewise often lower than 20 ng/mL.

In England and Wales, acute MI was found to be the cause of excess winter mortality (EWM). In all time periods, patients 75 years of age and older had the highest absolute EWM, and August saw the lowest fatality rates. The researchers hypothesized that 25-OH-D concentrations greater than 36 ng/mL could lower winter month death rates (20). Cannistraci et al. discovered that during the summer, a portion of STEMI shifts significantly to the nocturnal interval and the difference between the numbers of STEMI in the diurnal and nocturnal intervals is lessened. They called this occurrence "summer shift." This epidemiological investigation revealed a connection between vitamin D levels and the "summer shift." (21).

Spontaneous resolution of coronary thrombus and increased collateralization during ST-elevation MI were observed in patients with high vitamin-D levels (22). Lack of vitamin D contributed to the emergence of ST elevation-type MI (23). Similarly, lower vitamin-D levels were found in MI patients compared to those with stable coronary disease. According to Jarrah et al people with vitamin D deficiency have an increased risk of suffering an acute myocardial infarction (24). In the current investigation, we found that patients with STEMI had reduced vitamin-D levels. Lower vitamin-D levels, however, had no impact on the emergence of stent thrombosis in our investigation.

The earliest plaque rupture due to neoatherosclerosis following index stent implantation occurred after 1.6 years in drug-eluting stents (DES) implanted patients and after 2.5 years in bare metal stent (BMS) implanted patients. In our study, we observed stent thrombosis developing in fifty-three patients (60 %) after one year. In the first year, the cause of stent thrombosis may have been mispositioned and uncovered stent struts. Given that the cause of stent thrombosis in our study may be factors other than inflammation. Increased inflammation or vitamin D's protective impact against stent thrombosis were not observed.

3. The allergic inflammatory state: In our study, patients with stent thrombosis had higher basophil counts than MI patients without stent thrombosis. The cut-off value for the basophil count was 0.02. When the basophil count decreased beyond that level, the risk of developing stent thrombosis increased as much as 13-fold. Hypersensitivity developed due to probable uncovered metal struts and polymers may have caused an inflammatory reaction. Therefore, the increased inflammatory reaction may trigger thrombotic activation in the stent area. Studies on human pathology showed that 200 times more activated mast cells were detected at plaque ruptures than in undamaged coronary intima (3). Eosinophil accumulation in thrombus specimens was found at similar levels according to the timing of stent thrombosis and they were found in higher numbers with DES than with BMS, albeit not significantly higher (25).

Our study has some limitations. This study is an observational cross-sectional study. Seasonal change might affect our vitamin-D results. Only 60 % of the patients developed stent thrombosis after one year. Therefore, we might not have objectively evaluated the effect of inflammatory mediators on stent thrombosis. Because all patients in group 2 were included in our study during the winter season, the vitamin D levels in group 2 could be low. Despite these limitations, we applied strict exclusion criteria to obtain a homogeneous population.

In conclusion, stent thrombosis risk remains a significant issue despite advancements in stent technology. Recent studies have shown that the increased risk of stent thrombosis is caused by inflammatory mediators. However, the contribution of allergic inflammatory responses is controversial. According to our study, the combination of MPV and basophil count may be a predictor of the development of stent thrombosis. However, although low vitamin D levels increase the risk of native coronary thrombosis, this condition does not affect the risk of stent thrombosis. Also,

basophil counts below 0.02 increase the risk of stent thrombosis as much as 13-times. Large, prospective studies are needed for evaluating the relation between histopathologic changes and allergic, inflammatory mediators in patients with stent thrombosis.

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