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The Association Between Coronary Instent Restenosis and Eosinophil/Monocyte Ratio

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Abstract

Objectives: Although the incidence of coronary artery restenosis has decreased with the use of novel oral antiplatelet drugs and the use of new generation drug-eluting stents, it is a major problem that we encounter in daily practice due to the prolonged human lifespan and increasing numbers of percutaneous interventions. In this study, we investigated the association between instent restenosis, which is also an inflammatory process, and eosinophil/monocyte ratio (EMR), which is one of the new inflammatory indexes.

Materials and Methods: A total of 207 patients admitted with the acute coronary syndrome and underwent coronary angiography between June 2020 and June 2022 were analyzed retrospectively. The patients were divided into three groups: those with stent implantation and culprit lesion with stent restenosis (Group A), those with stent implantation and culprit lesion with the non-stent lesion (Group B), and patients without a stent and no critical lesion (Group C). Demographic characteristics, clinical presentations, comorbidities, hematological and biochemical parameters of the patients were evaluated.

Results: EMR was found to be statistically significantly lower in Group A compared in Group B (0.16±0.10 vs 0.40±0.9, p=0.041). There was also a statistically significant difference between the groups in terms of neutrophil (p=0.046) and high-density lipoprotein levels (p=0.010). Additionally, glucose levels at the time of admission were found to be significantly higher in Group A than in Group B (196.53±99.04 vs 159.57±84.31, p=0.048) and Group C (196.53±99.04 vs 140.41±89.66, p=0.001). There was no difference in terms of the levels of white blood cells, lymphocyte, monocyte, eosinophil, platelet, hemoglobin, total cholesterol, low-density lipoprotein, and triglyceride.

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Conclusion: Since a significant relationship has been shown between the instent restenosis of the culprit lesion and low EMR, EMR can be used as a simple tool to aid in the diagnosis of suspected restenosis in patients with stent implantation presenting with the acute coronary syndrome.

Keywords: Instent restenosis, eosinophil/monocyte ratio, EMR, acute coronary syndrome, admission blood glucose

Introduction

Coronary instent restenosis (ISR) is defined as the narrowing of the implanted stent in the lesion in the epicardial coronary artery[1]. Currently, the use of bare metal stents has been replaced by drug-eluting stents, and the development of a new generation drug-eluting stents, the incidence of ISR has decreased, but its incidence is still between 5 and 30%[1-3].

In the pathophysiology of ISR, elastic recoil in the early period, arterial remodeling, and neointimal hyperplasia appear to play a role in the long term. Additionally, incomplete coverage of the lesion, stent implantation in incorrect localization, stent fracture, and allergic reaction to nickel and molybdenum may also cause ISR[3-8].

As to pathophysiological mechanisms, arterial remodeling is one of the late-period mechanisms of ISR and is a negative arterial remodeling seen after balloon angioplasty. Although the exact mechanism of arterial negative remodeling is not known, there is partial improvement in this negative deformation after stent implantation[4,5].

Another mechanism involved in the formation of ISR is neointimal hyperplasia. There is mechanical structural destruction of the endothelium due to trauma caused by balloon inflation and trauma during stent implantation[4,5]. This destruction induces platelet adhesion, platelet activation, and cytokine release. The cytokine release stimulates the migration of smooth muscle cells to the intima and neointimal hyperplasia begins. The neointimal hyperplasia causes the late ISR formation in the long term[4,5].

A mononuclear cell-rich inflammation was also observed during mechanical damage to the endothelium during stent implantation. It is thought that the cells that create the inflammatory response here play a part in instent restenosis[4,5].

Considering the research on inflammatory markers in ISR, in which the inflammatory process also plays a role in its formation, a significant relationship was observed between the neutrophil/lymphocyte ratio and ISR[9]. Similarly, a significant correlation was observed between C-reactive protein (CRP) and stent restenosis[10].

Eosinophil/monocyte ratio (EMR) is one of the inflammatory markers that has been increasingly used. It has been suggested to be associated with ischemic cerebral events, decompensated heart failure, and acute ischemic coronary disease, prognosis, and survey[11-13]. There are very few studies investigating the association between EMR and ISR. In this study, we evaluated the relationship of EMR with ISR in patients with the acute coronary syndrome.

Materials and Methods

Study Design and Settings

The study was designed retrospectively. Patients who underwent coronary angiography with acute coronary syndrome between June 2020 and June 2022 were included. The ethics committee approval of this study was obtained from Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee (date: 07.06.2022, approval no: 125.17.14). In the study, data were obtained from hospital system records, cardiology clinical records, coronary angiography, and archive records.

Selection of the Participants

Three different groups were defined in this study. The first group (Group A), was the patients with acute coronary syndrome whose culprit lesion was instent restenosis, the second group (Group B) comprised those with the acute coronary syndrome who had a stent but whose culprit lesion was not instent restenosis, and the third group (Group C) was the patients with the acute coronary syndrome who did not have a significant lesion in their coronary arteries. The sample size was calculated using G-Power 3.1 and it was observed that a minimum of 69 patients should be included in each group. The patients were examined from 2022 to 2020, and the examination was terminated when there were 69 consecutive patients. Patients having both stent restenosis and critical lesions in the non-stent implanted vessels were excluded from the study. Additionally, patients with high CRP and erythrocyte sedimentation rate levels and those given antibiotics during hospitalization were excluded from the study.

Measurements and Outcomes

Instent restenosis was defined as angiographically ≥50% of stenosis within the stent implanted segment or inside a 5-mm segment distal or proximal to the stent[14]. Following the guideline, patients were grouped as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP)[15].

The complete blood count and the admission blood glucose were taken in the emergency room. The lipid profiles of the patients at hospitalization were examined.

Statistical Analysis

The SPSS 25.0 package program was used for data analysis in this study. Descriptive data on the demographic characteristics of the participants are given in the frequency tables. When the data of the study were analyzed in terms of normality assumptions, Kolmogorov-Smirnov values were determined as $p>0.05$. Additionally, the ANOVA test, one of the parametric tests, was applied to determine whether there was a significant difference between the laboratory data and the groups. In case of a significant difference between the groups, the LSD test, one of the post-hoc tests was used to determine between which groups the significance was. $P<0.05$ was considered statistically significant.

Results

The study included 207 patients, with 69 patients in each group. While the male gender dominated the study in Group A (n=46, 66.7%), and Group B (n=50, 72.5%), it was observed that females were more common in Group C (n=39, 58.5%) (Table 1). As a clinical presentation, NSTEMI was observed more frequently in Group A (n=30, 43.5%), UAP in Group B (n=34, 49.3%) and NSTEMI in Group C (n=44, 63.8%) (Table 1).

The prevalence of diabetes mellitus was 47.8% (n=33) in Group A, 31.9% (n=22) in Group B, and 23.2% (n=16) in Group C. Hypertension was present in 76.8% (n=53) patients in Group A, 91.3% (n=63) patients in Group B, and 42% (n=29) patients in Group C. The frequency of hyperlipidemia was 43.5% (n=30) in Group A, 55.1% (n=38) in Group B, and 14.5% (n=10) in Group C (Table 1).

As laboratory parameters, there was a statistically significant difference between the groups in terms of EMR (p=0.048). The Post hoc test revealed a statistically significant difference between Group A and Group B (p=0.041) (Table 2).

There was also a statistically significant difference in terms of blood glucose values at the time of admission (p=0.001). After the Post hoc test was performed, a statistically significant difference was shown between Group A and Group B (p=0.048), and between Group A and Group C (p=0.001) (Table 2).

There was a statistically significant difference between the groups in terms of neutrophil values (p=0.046). According to the Post hoc test, a statistically significant difference was observed between Group A and Group C (p=0.047) (Table 2).

Table 1. Distribution of demographic and clinical data of the patients

		ISR + Group A		Had a stent without ISR Group B		Do not have a significant lesion Group C	
Variable		**n**	**%**	**n**	**%**	**n**	**%**
Gender	Male	46	66.7	50	72.5	30	43.5
	Female	23	33.3	19	27.5	39	58.5
Clinical presentation	STEMI	19	27.5	14	20.3	25	36.2
	NSTEMI	30	43.5	21	30.4	44	63.8
	UAP	20	29.0	34	49.3	0	0.0
DM	No	36	52.2	47	68.1	53	76.8
	Yes	33	47.8	22	31.9	16	23.2
HT	No	16	23.2	6	8.7	40	58.0
	Yes	53	76.8	63	91.3	29	42.0
HL	No	39	56.5	31	44.9	59	85.5
	Yes	30	43.5	38	55.1	10	14.5
CAD	No	0	0.0	4	5.8	69	100.0
		69	100.0	65	94.2	0	0.0

Group A; was the patients with acute coronary syndrome whose culprit lesion was instent restenosis
Group B; was the patients with acute coronary syndrome who had a stent but whose culprit lesion was not instent restenosis
Group C; was the patients with acute coronary syndrome who do not have a significant lesion in their coronary arteries
STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, UAP: Unstable angina pectoris, DM: Diabetes Mellitus, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease

Table 2. Comparison of laboratory findings by groups

	ISR + Group A Mean ± SD n=69	Had a stent without ISR Group B Mean ± SD n=69	C- Do not have a significant lesion Group C Mean ± SD n=69	p	Post-hoc
EMR	0.16±0.10	0.40±0.9	0.32±0.34	**0.048**	1-2
Glucose (mg/dL)	196.53±99.04	159.57±84.31	140.41±89.66	**0.001**	1-2.3
WBC (10^9/L)	10.22±3.26	9.74±3.19	8.98±2.92	**0.068**	
Lymphocyte (10^9/L)	2.21±1.36	2.4±1.44	2.03±0.88	**0.223**	
Monocyte (10^9/L)	0.66±0.28	0.65±0.31	0.66±0.30	**0.990**	
Eosinophil (10^9/L)	0.15±0.14	0.22±0.37	0.17±0.15	**0.284**	
Neutrophil (10^9/L)	7.14±2.88	6.32±2.24	6.08±2.71	**0.046**	1-3
Platelet (10^3u/L)	274.87±84.85	264.57±84.16	260.04±71.19	**0.540**	
Hemoglobin (g/dL)	13.62±1.88	13.91±2.01	13.94±1.86	**0.556**	
Total cholesterol (mg/dL)	185.88±55.64	184.08±49.38	193.07±39.92	**0.520**	
LDL (mg/dL)	117.51±45.36	112.91±41.49	113.68±35.98	**0.780**	
Triglyceride (mg/dL)	137.82±88.83	166.67±102.44	168.37±99.75	**0.119**	
HDL (mg/dL)	41.54±8.44	40.06±10.35	51.26±37.91	**0.010**	3-1.2

ANOVA test, post-hoc: LSD test applied. p<0.05 statistically significant.
EMR: Eosinophil/monocyte ratio, WBC: White blood cell, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

High-density lipoprotein (HDL) value showed a statistically significant difference between the groups (p=0.010). According to the post-hoc test, a statistically significant difference was observed between Group C and Group A (p=0.014) and between Group C and Group B (p=0.039) (Table 2).

Among the groups, white blood cell (WBC) (p=0.068), lymphocyte (p=0.223), monocyte (p=0.990), eosinophil (p=0.284), platelet (p=0.540), hemoglobin (p=0.556), total cholesterol (p=0.520), low-density lipoprotein (LDL) (p=0.780), triglyceride (p=0.119) values did not show a statistically significant differences (Table 2).

Discussion

In our study, one of the main findings was that the EMR was found to be significantly lower in patients with previous stent implantation presenting acute coronary syndrome, with the culprit lesion stent restenosis, compared with those without stent restenosis. Additionally, the admission blood glucose values of the patients were found to be significantly higher in those with stent restenosis as the culprit lesion. The neutrophil count was found to be higher in the patients with stent restenosis than in patients without critical lesions. In patients without critical lesions, HDL values were found to be higher than in those with critical lesions.

Although the stent restenosis rates have decreased with the use of new generation drug-eluting stents and new oral antiplatelets, it is still a major problem in daily practice. Although in the previous studies, ISR was mostly presented with non-MI conditions, the frequency of presentation with acute MI conditions has increased in recent studies[16-19]. Since patients with stable angina pectoris were excluded from our study, we can only state a frequency among acute coronary syndrome groups. As a result, NSTEMI was seen the most frequent in the group with ISR. Our findings are consistent with a recent ISR and acute coronary syndrome study[19].

Inflammation is thought to play a part in the formation of stent restenosis[4]. There are many studies on neutrophils, lymphocytes, and monocytes that play a role in this inflammation. The number of studies on eosinophils, which is a cell whose role in inflammation is unclear, is few. It is thought that eosinophils may cause acute coronary syndrome by releasing proinflammatory and proanticoagulant proteins[20]. Additionally, it has been suggested that eosinophil count and eosinophil/lymphocyte ratio (ELR) are inflammatory markers that can be used in risk assessment in coronary artery disease[21]. Bilik et al.[22] reported that ELR was found to be significantly higher in patients with stent restenosis in their study.

It is thought that monocytes cause stent restenosis via macrophages[23]. It is thought that macrophages produce foam cells from oxidized LDL and the formed foam cells cause inflammatory factor release and lead to stent restenosis[24]. It has been reported that high monocyte counts play a role in plaque progression, and a high ratio of monocyte to HDL (MHR) can be used as an indicator of inflammation[25,26]. In the study by Chen et al.[27] it was observed that the count of monocytes and ratio of monocytes to HDL (MHR) in patients with stent restenosis was higher than in those without stent restenosis.

EMR is a recently used inflammatory marker obtained by dividing the eosinophils by the monocytes. It has been observed that a low EMR value is associated with poor prognosis in acute ischemic stroke events[11]. When we reviewed the cardiac studies on EMR, Chen et al.[12] showed that low EMR is associated with poor prognosis in patients with decompensated heart failure. Additionally, Deng et al.[13] showed that patients with STEMI with low EMR had poor prognosis and mortality in the 1-month and long term. In our study, the EMR of patients presenting with acute coronary syndrome due to stent restenosis in patients with had a stent was found to be significantly lower than compared the other groups.

Studies have shown that neutrophil, one of the cells involved in inflammation, also increase coronary ischemia and infarction, especially in post-intervention reperfusion[28,29]. In our study, the neutrophil count was found to be significantly higher in patients with instent

restenosis than in patients without significant coronary stenosis.

It has been shown that stress-induced hyperglycemia increases cardiovascular events in both diabetic and non-diabetic patients in the short and long term and increases major adverse cardiovascular and cerebrovascular events in patients with STEMI[30,31]. It has been reported that the high-admission glucose level at the time of admission is associated with in-hospital adverse events and length of stay in the hospital in NSTEMI[32]. When we examine the glucose studies for stent restenosis, researchers have shown that HbA1c and fasting glucose are among the values predicting stent restenosis[33]. In our study, the admission blood glucose level was significantly different. In patients with ISR, admission blood glucose was found to be higher than the group without the stent with the culprit lesion and the group without coronary lesion. Since our study was retrospective and patients presenting with acute coronary syndrome were not routinely tested for HbA1c, we could not comment on fasting glucose and HbA1c.

One of the risk factors for coronary artery disease is dyslipidemia. The relationship between high LDL levels and low HDL levels and coronary artery disease is known[34]. Yanık et al.[35], when examining patients with and without stent restenosis, showed that there is a relationship between low HDL cholesterol and stent restenosis. In our study, when ISR was compared with patients without significant coronary lesions, low HDL was observed in the ISR group.

Study Limitations

Our study has several limitations. First, the study was designed as retrospective. Another limitation is whether the previously implanted stent was drug-eluting or bare metal in patients stents. Additionally, it is not known whether the patients had a history of allergic disease or an infectious disease at the time of stenting. Finally, it is recommended to use of optical coherence tomography and intravascular ultrasound for stent restenosis and typing, but only coronary angiography has been used for stent restenosis because to the lack of these devices.

Conclusion

In our study, a low EMR was observed in an acute coronary syndrome patient who had a stent, in those with instent restenosis of the culprit lesion. The high glucose level at the time of presentation accompanying these findings is proof of how closely stent restenosis is associated with inflammation and impaired metabolic process.

Ethics

Ethics Committee Approval: Ethics committee approval of this study was obtained from Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee (date: 07.06.2022, decision no: 125.17.14)

Informed Consent: No written informed consent form was obtained from patients because the study was retrospective.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Şabanoğlu C, Polat E, Design: Şabanoğlu C, Polat E, Yüce Eİ, Data Collection and/or Processing: Polat E, Yüce Eİ, Analysis and/or Interpretation: Şabanoğlu C, Polat E. Literature Search: Şabanoğlu C, Polat E, Yüce Eİ, Writing: Şabanoğlu C, Polat E, Yüce Eİ.

Conflict of Interest: The authors have no conflicts of interest to declare.

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