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The value of peripheral blood eosinophil count in predicting in-stent restenosis in patients with stable angina pectoris undergoing drug eluting stenting

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Introduction. In-stent restenosis (ISR) remains a major limitation of percutaneous coronary intervention (PCI). A role for peripheral blood cells as major regulators of immune and inflammatory systems has been proposed. We aim to evaluate the relationship between eosinophil count and development of restenosis after drug-eluting stent (DES) implantation.

Methods. In this prospective study, all consecutive patients undergoing elective DES implantation for chronic stable angina (CSA) in a university-affiliated heart center within a 6-month period were enrolled and followed for another 6 months. Complete blood count with differentiation was performed 6 weeks after the index procedure. During the follow-up period, the cohort of patients who developed ISR was compared to the cohort of patients without ISR, descriptively and the total number of eosinophilic white cells was used to predict the occurrence of ISR.

Results. 153 men and 48 women with CSA underwent PCI with DES implantation, from which, 26 patients needed repeat coronary angiography for recurrent symptoms. There was an established ISR in 17 (8.5%) patients. The total number of eosinophils in their peripheral blood was 267 ± 132 cells/μL in patients with ISR, significantly higher than the number of eosinophils in those without ISR 174 ± 133 cells/μL (P-value < 0.010). Eosinophil count remained an independent predictor of ISR in multivariate analysis as the eosinophil count value over 242 cells/μL had sensitivity of 66.7% and specificity of 84.5% for the presence of ISR.

Conclusion. The total number of eosinophils, counted 6 weeks after DES implantation, prevails as the sole predictor of ISR occurrence in our study. This suggests an association between immune sensitivity reaction to DES material and development of ISR in patients after PCI.

Key words: Eosinophil; in-stent restenosis; stent; complete blood count; percutaneous coronary intervention.

INTRODUCTION

Percutaneous coronary intervention (PCI) has become the standard method of myocardial revascularization for critical stenosis of coronary arteries [1, 2]. However, despite advances in the field of coronary intervention, with a prevalence of 10%, in-stent restenosis (ISR) remains a major limitation [3]. ISR typically occurs within 6 months of stenting. Development of ISR has reduced significantly by introduction of drug-eluting stents (DES). This could be attributed to the anti-inflammatory and anti-proliferative effects of DES stents [4, 5]. However, ISR after DES implantation still occurs [6, 7].

Fibrin proliferative processes as well as inflammatory responses to the arterial wall injury are among the proposed mechanisms for ISR [8, 9]. The presence of microvascular disease such as that seen in diabetes mellitus, vascular wall trauma, the amount of the residual plaque burden and the length/diameter ratio of the implanted stents contribute to the process ISR formation [10, 11]. Some scientists have investigated the role of peripheral blood cells in ISR as the major regulators of immune and inflammatory systems. All blood granulocytes, especially neutrophils are known to play a crucial role in the inflammatory reactions following balloon angioplasty [12]. Predominance of monocytes/macrophages in inflammatory response to bare metal stents (BMS) was shown in previous studies [13, 14]. T-cells and B-cells are both present in the plaques isolated from the areas of restenosis after DES implantation [15].

Additionally, eosinophils and giant cells widely infiltrate tissues adjacent to metallic material particularly polymeric stent components [14, 16]. In one study an increase in the eosinophil count in the peripheral blood during the restenosis period was observed [17]. Serum levels of eosinophil-secreted cytokines such as eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase, or eosinophil-derived neurotoxin could be used as the biomarkers of intravascular activation of eosinophils [18, 19]. However, there has been no robust

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study to recommend using the information derived from complete blood count (CBC) in predicting ISR. The aim of this study was to evaluate the predictive value and the cut-off value of eosinophil count in the development of restenosis after DES implantation for chronic stable angina. We hypothesized that a certain count of eosinophils in peripheral blood could predict the development of ISR after PCI with DES implantation with a significant sensitivity and specificity.

MATERIAL AND METHODS

This was a prospective study done between November 2015 and June 2016, consisting of 204 consecutive patients who underwent elective DES implantation at University-affiliated heart center in Tabriz, Iran. Institutional review board approved the study protocol for its scientific and ethical merits. Written informed consents were obtained from all the patients for their participation and follow-up.

Demographic characteristics including age, gender, drug history, past medical history, smoking history, body mass index and family history of CAD, clinical and laboratory findings along with angiographic parameters were recorded. Patients who had acute coronary syndrome in the preceding 2 months, those with a history of coronary artery bypass surgery, ejection fraction < 40%, congestive heart failure, stage III or higher chronic kidney disease, secondary eosinophilia due to parasitic infection, liver failure, known malignancy, known history of allergy and asthma, additional revascularizations other than coronary artery stenting (either percutaneous or surgical) before the index procedure, neurological or mental disorders, and any other acute or chronic inflammatory disease which could impact complete blood count were excluded. We also did not include patients who could not complete the 6-month follow-up period.

The indication for coronary angiography was the presence of ischemic symptoms or evidence of myocardial ischemia in non-invasive tests at the discretion of the managing cardiologist. Patients underwent follow-up for a period of 6 months after the stenting procedure. Cypher^{TM} stents (Cordis Inc., Miami Lakes, FL) or Taxus^{TM} stents (Boston Scientific Inc., Natick, MA) were implanted at the discretion of the interventional cardiologist decision. The first follow-up visit was scheduled 6 weeks after the date PCI or recurrence of ischemic symptoms. During the follow-up period, patients who developed ischemic symptoms or positive non-invasive testing underwent repeat coronary angiography at the discretion of managing cardiologist for evaluating ISR.

The primary endpoint for this study was development of in-stent restenosis (ISR) that was confirmed by repeat coronary angiography. ISR was defined as a stenosis inside the stent or within 5 mm distance from its proximal or distal margins with > 50% decrease in luminal diameter. Patients who had ISR in the coronary angiogram were compared to those 1) asymptomatic patients who did not undergo repeat coronary angiography and 2) who demonstrated patent implanted stent in coronary angiograms despite the presence of non-specific symptoms, then analyzed and compared between ISR group and the rest of the study population (control group).

At the time this visit a complete hematologic analysis was performed from all patients. Hematologic variables included platelet count (cells/μL), platelet aggregation, mean platelet volume (MPV) (fL), and platelet distribution width (PDW), hemoglobin (g/dL), mean corpuscular volume MCV (fL) and red cell distribution width (RDW), along with flow-cytometric differential count of white blood cells (WBC).

Statistical analysis

Kolmogorov-Smirnov test was used to examine the normality of distribution for continuous variables. If normality was rejected, Mann-Whitney U test was used for comparing the groups. Continuous variables with normal distribution were analyzed with independent two-sample t-tests and were reported as mean ± standard deviation. Categorical variables were reported as frequency (percentage) and compared with Chi square tests as appropriate. Multivariate binary logistic regression was used to identify the independent predictors of ISR using variables with a p-value of less than 0.10 in univariate analysis (gender, hypertension and eosinophil count). Receiver operating characteristics (ROC) curve was plotted to identify the cut-off value of eosinophil count for the occurrence of ISR. Collected information was analyzed using Statistical Program for Social Sciences SPSS 24.0 (IBM®, Chicago, IL). A P-value less than 0.05 was considered as statistically significant.

RESULTS

During the study period, 204 patients were initially enrolled. During the follow-up period 2 patients had sudden cardiac death, one patient died of non-cardiac causes and eventually 201 patients

finished follow-up period and entered the study. Majority of patients (76%) were male with average age of 58 ± 10 years old. Mean follow-up period was 6.5 months. Frequency distribution for single, double and triple vessel coronary disease were 37.3%, 40.8% and 17.9%, respectively. A total of 347 stents were implanted in 201 patients. During the follow-up period, 26 patients underwent repeat coronary angiography because of typical chest pain or positive non-invasive testing. ISR was described in 17 patients (8.5%) and in the remaining 9 patients no ISR was attributed to the recurrence of symptoms.

Medication history, demographics and clinical characteristics of patients with and without ISR have been depicted in Table 1. There was a statistically significant difference between two groups in terms of prevalence of hypertension (P = 0.005) and eosinophilia (P = 0.002). Also we found a strong trend for lower frequency of ISR occurrence among female patients but this difference did not reach a statistical significance (P = 0.071). Patients were otherwise similar in age, body habitus, the frequencies of co-morbid diseases and the types of medications they were treated with. Laboratory values from the first follow-up visit were compared in the two groups according to the presence of ISR (Table 2). Other than the number of eosinophils in the peripheral blood, remaining hematologic and biochemical variables were similar between the two groups. Median number of eosinophils was 260 with an interquartile range of 184 cells/μL blood in patients with ISR while it was 150 [110] among asymptomatic patients (P = 0.005). Eosinophil count of the peripheral blood was a strong predictor of ISR with a predictive value of 0.745 ± 0.032 (Figure 1). The cut-off value for the number of blood eosinophils in predicting the occurrence of ISR was 242 cells/μL with a sensitivity of 66.7% and specificity of 84.5%.

Table 1
Baseline characteristics of the study population

Variables		(+) ISR (N = 17)	(-) ISR (N = 184)	Odds Ratio 95% Confidence Interval	P-value
Age		56 ± 11	58 ± 9	1.03 (0.98 – 1.08)	0.299
Gender	Male	16 (94.1%)	137 (74.5%)	5.49 (0.71 – 42.52)	0.079
	Female	1 (5.9%)	47 (25.5%)		
ACEI/ARB		11 (64.7%)	87 (47.3%)	2.04 (0.73 – 5.76)	0.169
Statin Drugs		14 (82.4%)	157 (85.3%)	0.80 (0.22 – 2.98)	0.724
Calcium Channel blockers		2 (11.8%)	31 (16.8%)	0.66 (0.14 – 3.02)	0.744
Beta blocker		14 (82.4%)	149 (81.0%)	1.10 (0.30 – 4.02)	1.000
Hypertension		14 (82.4%)	84 (45.7%)	5.56 (1.54 – 20.00)	0.005
Hyperlipidemia		15 (88.2%)	160 (87.0%)	1.12 (0.24 – 5.26)	0.655
Current Smoking		2 (11.8%)	39 (21.2%)	0.50 (0.11 – 2.26)	0.533
Family history of Coronary Disease		0 (0.0%)	8 (4.3%)	Not Calculated	1.000
Diabetes mellitus		7 (41.2%)	46 (25%)	2.10 (0.76 – 5.84)	0.158
Height (cm)		168 ± 8	167 ± 9	0.98 (0.93 – 1.04)	0.512
Weight (kg)		75.7 ± 10.9	77.0 ± 13.1	1.01 (0.97 – 1.05)	0.691
BMI (kg/m^2)		26.7 ± 2.8	27.9 ± 5.9	1.07 (0.92 – 1.24)	0.387

ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: angiotensin receptor blocker

Table 2
Univariate analysis of various hematologic and laboratory variables on in-stent restenosis

Variables	Odds Ratios 95% Confidence Interval	(+) ISR (N = 17)	(-) ISR (N = 184)	P-value
Hemoglobin (g/dL)	0.82 [0.55-1.22]	14.6 [1.0]	14.1 [1.5]	0.218
Mean Corpuscular Volume (fL)	0.95 [0.86 – 1.06]	86.4 [3.6]	85.7 [6.1]	0.276
Red Cell Distribution Width (%)	0.85 [0.44 – 1.63]	14.4 [0.4]	14.2 [1.2]	0.205
Platelet (Counts/nL)	1.006 [0.995 – 1.017]	193 [48]	209 [84]	0.289
Mean Platelet Volume (fL)	0.76 [0.49 – 1.19]	10.3 [1.0]	10.1 [1.0]	0.447
Platelet Distribution Width (%)	1.04 [0.96 – 1.13]	42.6 [6.0]	45.1 [7.0]	0.384
White Blood Cell (Cells/μL)	1.000 [1.000 – 1.001]	5,420 [1,270]	6,220 [2,178]	0.180
Neutrophil Count (Cells/μL)	1.000 [1.000 – 1.001]	3,080 [630]	3,540 [1,380]	0.141
Lymphocyte Count (Cells/μL)	1.001 [1.000 – 1.002]	1,590 [1,120]	1,950 [718]	0.292
Neutrophil-Lymphocyte Ratio	1.12 [0.66 – 1.90]	1.77 [1.00]	1.78 [0.80]	0.681
Monocytes Count (Cells/μL)	1.001 [0.997 – 1.006]	290 [210]	360 [175]	0.632
Eosinophil Count (Cells/μL)	1.003 [1.001 – 1.006]	260 [184]	150 [110]	0.002
Basophil Count (Cells/μL))	1.007 [0.990 – 1.024]	60 [30]	50 [30]	0.159
Creatinine	1.21 [0.17 – 8.71]	1.09 [0.01]	1.05 [0.03]	0.853
Blood Glucose (mg/dL)	1.002 [0.994 – 1.004]	138 [57]	106 [51]	0.679

In all variables, the normality was rejected by P values <0.05 in Kolmogorov-Smirnov test therefore Mann-Whitney U tests were used to compare the two groups. Odds ratios were calculated by binary logistic univariate tests.

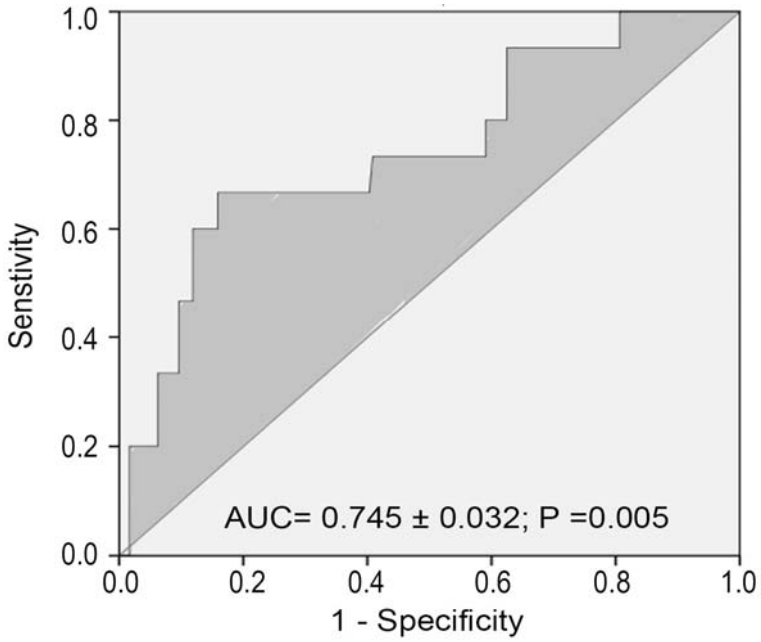

Figure 1. Receiver operator characteristics curve of eosinophil percentage value to predict in-stent restenosis. Area under the curve (AUC) = 0.75 (0.70-0.83 CI:95%).

A multivariate binary logistic regression analysis was performed to investigate the interactive role of gender (P = 0.071), hypertension (P = 0.002) and eosinophil count (P = 0.005) in the occurrence of ISR (Table 3). Gender differentiation lost its association with ISR, while hypertension and eosinophil counts remained independent predictors of ISR. Prior history of hypertension was associated with 20-fold increase in the risk of ISR. Additionally, for every 10 cells/μL increase in the peripheral eosinophils, as assessed 6 weeks after implantation, the risk of ISR increased by 3% (P = 0.023).

Table 3
Multivariate analysis for identifying variables that predict occurrence of in-stent restenosis

	Coefficient	S.E.	P-value	Odds Ratio	95% C.I. for Odds Ratio	
					Lower	Upper
Eosinophils (cells/μL)	0.003	0.002	0.023	1.003	1.000	1.006
Male/Female	18.480	5591.218	0.997	1.061E+08	0.000	
Hypertension	3.058	1.194	0.010	21.277	2.048	221.056
Constant	-23.760	5591.218	0.997	0.000		

DISCUSSION

Our results showed that eosinophil count measured 6 weeks after PCI has a significant association with the development of ISR within 6-months after DES implantation. We did not found any relation between ISR and other marker of systemic inflammation such as the ratio of neutrophils to lymphocytes or the state of platelet aggregation. Our findings suggest a possible role of hypersensitivity or allergic reactions in ISR phenolmenon. The exact role of allergy in cardiovascular disease is not clear and needs more investigations. Some studies have shown the role of allergy and allergic acute coronary syndrome (Kounis syndrome) in patients with ischemic heart disease [20, 21]. Recently a population-based, matched cohort study showed that patients with previously diagnosed allergic rhinitis had significantly lower risk for myocardial infarction (P < 0.001) [22].

Previous studies have investigated the role of contact allergy to nickel, molybdenum ions as materials of stainless-steel stents. Koster *et al*. showed a significant correlation between allergic reaction to nickel and molybdenum diagnosed with patch test [23]. However, other studies were not able to establish an association between results of nickel patch test and ISR [24-26]. In a case report by Otsuka *et al.* histopathological study of the atheroma removed by endarterectomy in a patient

with severe ISR showed abundance of lymphocytes and eosinophils, favoring a hypersensitivity vasculitis [27]. In another case report by Yagi *et al.*, a severe eosinophilia (differential count of 48% eosinophils in peripheral blood) in an elderly man with angiographically documented ISR following implantation of DES. They suggested eosinophilia as a hypersensitivity type 1 immune reaction to the implant that had led to a vascular injury and development of ISR [28].

Local eosinophilic infiltration is not uncommon at the site of DES implants. This is a localized foreign body reaction that lasts about six weeks, the time needed for the surface of the stent to be covered by the growth of the intimal layer. The process of re-endothelialization limits the inflammatory response by decreasing the exposure of immune system to the antigenic material in DES implants within 12 weeks after implantation. Smooth muscle cells, T lymphocytes and macrophages are usually seen during this healing process [29]. Rittersma *et al*. studied 16 patients with restenosis following balloon angioplasty and 16 patients who developed ISR after stenting. Eosinophils were significantly increased in the tissue obtained from ISR group (P = 0.012) compared to those with restenosis after angioplasty [30]. Takashima *et al*. examined histo-pathological characteristics of atheromas removed from 4 different types of stents. This study linked significant eosinophilic infiltrations (hypersensitivity type I reaction) of the atheroma from paclitaxel-eluting stents and everolimus-eluting stents, while in atheromas from bare-metal stent, a neo-atherosclerotic process was the dominant pattern [31].

Similar to our findings, Gabbasov *et al.* demonstrated a higher prevalence of ISR in patients with blood eosinophil count greater than 170 cells/μL ($p < 0.001$) [32]. The reported cut-off value in their study sample was, however, lower than 242 eosinophils/μL that has been reported here. In addition to peripheral eosinophilia, high levels of ECP were described in the patient who developed ISR following DES implantation (P-value = 0.017) indicating activation of these inflammatory cells among these patients [33]. However, these investigators failed to show elevated levels of high-sensitive C-reactive proteins (hs-CRP) and Immunoglobulin E levels in patients with ISR.

Taxus® and Cypher® stents contain non-erodible polymers that are antigenic to the host's immune system resulting in a local hypersensitivity reaction. Comparable to our findings in univariate analysis, Mehilli *et al*. reported a 23% decrease in risk for ISR (OR = 0.77, 0.63 to o.93 CI 95%) among women [34]. In an animal model of ISR, the thickness of neo-intima after balloon injury to the carotid artery was significantly lower in female rats than that in male rats ($P < 0.05$) [35]. Removal of the ovaries of female rats increased formation of neointima ($P < .05$). In addition to stent material, other substances could possibly trigger a hypersensitivity type reaction. For example, male rats response to c-*myc* was greater and more rapid although c-*myc* mRNA levels were increased in both male and female rats. Using 17β-estradiol in oophorectomized rats resulted in a 60% decrease in myointimal response to vascular injury. Moreover, two types of estrogen receptors are expressed on the membrane of eosinophils. Estradiol-17ß and diethylstilbestrol can both influence migration and degranulation of these inflammatory cells [36]. Decreased eosinophil count in the peripheral blood with or without possible loss of their membrane-bound receptors can limit its migration into the tissues. Eosinophils increase serum matrix metalloproteinase (MMP)-9 through the inflammatory process with TNFα. MMPs are thought to play an important role in interstitial matrix turnover [37]. Katsaros *et al*. have shown that in patients with implanted DES, increased serum levels of MMP-2 and MMP-9 are significant predictors of ISR [38].

There are other theories regarding eosinophil count, gender and risk factors of cardiovascular diseases. Fukui *et al*. evaluated 783 patients with type 2 diabetes. They investigated the correlation between eosinophil count and urine albumin excretion as a risk factor of cardiovascular disease. They showed that systolic hypertension, serum triglyceride and albumin excretion rate had a significant positive correlation with serum eosinophil count in men. In women no association was found between serum eosinophils and albumin excretion rate [39]. In our study, both gender and hypertension had influenced the occurrence of ISR, but this association with male gender was not independent. It is possible that gender differences in ISR rate depend on eosinophil count differences or the prevalence of hypertension in men and women.

As it is with most of single-center studies, this also suffered from a relatively small sample size. Further studies with a larger number of participants may be able to answer more questions regarding the role of gender, where our study lacks the necessary power to examine. We could not repeat angiography in all patients due to ethical concerns. Since there are only 17 patients with ISR,

inclusion of more two independent variables may obscure findings due to statistical errors. This study only examines the number of eosinophils in the peripheral blood and may not comment on their state of activation and the nature of cellular infiltration within the ISR-producing atheromas.

We conclude that absolute eosinophil count and its percentage measured 6 weeks after DES implantation reliably predicts the occurrence of ISR with a modest sensitivity and a reasonable specificity. This test may not be used as a single screening tool because of its relatively lower sensitivity; however, it may be more useful when it is used along with other markers of inflammation. From a pathophysiological standpoint, the presence of peripheral eosinophilia suggests that the extent of allergic reactions to the material in DES implants may act as the initiating step towards development of ISR and recurrence of ischemic symptoms following an elective PCI.

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Introducere. *Restenoza rămâne o problemă majoră a intervenţiilor coronariere percutanate pentru care a fost propus un rol al celulelor periferice drept mecanism. Obiectivul studiului a fost de a evalua legătura dintre numărul de eozinofile şi dezvoltarea restenozei după implantarea unui stent tip DES ("Drug eluting stent").*

Metode. *A fost realizat un studiu prospectiv pe o durată de 6 luni, toţi pacienţii cu angină stabilă care au fost candidaţi pentru implantarea DES dintr-un centru universitar. La 6 săptămâni le-a fost realizată o hemogramă de control. Pacienţii care au dezvoltat stenoză au fost comparaţi cu cei ce nu au dezvoltat stenoză.*

Rezultate. *153 de barbaţi şi 48 de femei cu angină stabilă au realizat PCI cu implantare DES din care 26 de pacienţi au necesitat repetarea angiografiei pentru simptome recurente. 8.5% (17 pacienţi) au avut restenoză. Numărul total de eozinofile circulante a fost de 267 ± 132 eozinofile/μL la pacienţii cu stenoză, semnificativ statistic mai mare comparativ cu pacienţii fără restenoză (174 ± 133 eozinofile/μL $p < 0.01$). Numărul de eozinofile a rămas predictor independent al stenozei în analiza multivariată iar un număr de eozinofile peste 242/μL a avut sensibilitatea de 66.7% şi specificitatea de 84.5% de a prezice stenoza.*

Concluzii. *Numărul total de eozinofile la 6 săptămâni după implantarea DES a prezis restenoză. Acest aspect sugerează legătura dintre sensibilizarea la materialul folosit pentru stent şi dezvoltarea ulterioară a stenozei la aceşti pacienţi.*

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