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Investigating the Association Between Serum Pro- and Anti-Inflammatory Cytokines Concentration and In-Stent Sestenosis : A Case Control Study

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ABSTRACT

Introduction : It has been shown that angioplasty and endovascular stent deployment, used after coronary revascularization, are associated with an inflammatory response. Inflammation has a key role in the complications of atherosclerotic plaque, coronary artery disease (CAD) and in-stent restenosis (ISR). The objectives of the present study was to investigate serum levels of 12 pro/anti-cytokines and growth factors and their relationship with restenosis.

Methods: A total of 244 subjects were recruited in current study including unrelated patients who previously underwent coronary stent implantation (between 2014 and 2017) and were subsequently indicated for coronary angiography. According to angiography results patients were allocated into two groups: cases with stenosis more than 50% within the stent (N=79) and controls with stenosis less than 50% within the stent (N=165). Serum was separated by centrifuging the blood for 15 min at 1000 rpm. Serum cytokines levels including IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, EGF, and VEGF were measured using an EV 3513 cytokine biochip array (Randox Laboratories, Crumlin, UK).

Results: The mean age of the NISR and ISR groups were 62.47±9.2 and 59.49±8.48 years, respectively. The diabetes frequency was significantly higher in the ISR group (55.1%) compared with NISR group (30.9%) ($p<0.001$). There was no significant difference in levels of cytokines between the two groups ($p>0.05$).

Conclusions: The results showed that serum levels of pro/anti-inflammatory cytokines and growth factors did not have a significant difference between NISR and ISR study groups.

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Introduction

Coronary artery disease (CAD) comprise conditions affecting the blood vessels (1). Angioplasty and endovascular stent deployment is a major therapeutic strategy used after coronary revascularization and is associated with an inflammatory response (2-4). Stenosis more than 50% within the coronary stent is defined as angiographic restenosis. Clinical stenosis is the return of angina and need to revascularization. Nearly half of patients who have angiographic restenosis do not have clinical symptoms (5). Angioplasty may be associated with vascular damage and stimulates the migration, proliferation and inflammation of smooth muscle cells (2, 3). Inflammation plays an important role in the formation, progression and complications of atherosclerotic plaque, CAD and in-stent restenosis (ISR) (6, 7). Studies have shown that serum cytokines are associated with severity of CAD (8). Several cell types are involved in the production of inflammatory cytokines: e.g. leukocytes, hepatocytes, cardiac myocytes, adipocytes and endothelial cells (1). High serum cytokine concentrations, including serum TNF-α, have been shown in coronary arteries after angioplasty and stent restenosis is associated with secretion of vasoactive and growth factors, and may lead to the formation of a thrombus (8-10).

Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1, IL-2, IL-8, IL-17, interferon-gamma (IFN-ɣ) and anti-inflammatory cytokines such as IL-1 receptor antagonist and IL-10 are involved in the inflammatory process associated with atherosclerosis (6, 10-12). Inflammatory cytokines are important regulators of cell signaling and are involved in autocrine, paracrine and endocrine signaling pathways (10, 13, 14). Increased levels of growth factors are also related to inflammation associated angiogenesis, in the formation and progression of atherosclerotic plaque and its instability (15). Moreover, studies have shown a relationship between high levels of inflammatory cytokines including IL1, IL-6, TNF-α, IFN-ɣ with restenosis following angioplasty (7). Chalikias et al. also proposed that an imbalance in pro- and anti-inflammatory cytokine levels may be involved in recurrent cardiovascular events while cytokine ratios such as the IL-18/IL-10 ratio, was an independent predictor of coronary syndrome (16).

The objectives of the present research was to investigate serum levels of 12 cytokines and their relationship to restenosis after percutaneous coronary intervention (PCI) in Iranian population.

Material and Methods

Study population

The study participants comprised a group of 244 Iranian patients who previously underwent coronary stent implantation (between 2014 and 2017) for stable angina, or unstable angina, and were subsequently indicated for angiography because of recurrent exertional angina according to 2011 ACCF/AHA/SCAI guideline (17). Participants were allocated into two groups according to their angiography report. Seventy nine cases with stenosis more than 50% within the stent and 165 controls with stenosis less than 50% within the stent. Demographic and past medical history were recorded into a questionnaire. Patients with stent thrombosis in the first month after angioplasty, autoimmune disorder, active cancer, thrombophilia or chronic kidney disease were excluded. Arterial blood from femoral or brachial catheter was drawn into a tube without anticoagulant, before angiography procedure. Serum was separated and stored at –80°C.

Cytokine Assay

Serum cytokines including IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, EGF, and VEGF were determined using an EV 3513 cytokine biochip array (Randox Laboratories, Crumlin, UK) and competitive chemiluminescence immunoassays according to the manufacturer's instructions, using the Randox Evidence Investigator, as described previously (18) .

Statistical analysis

Statistical analysis was carried out using version 11.0 of SPSS (SPSS Inc., IL, USA). Continuous and categorical variables are reported as mean ± standard deviation (SD)

and frequency percentage, respectively. A Student's T test was applied for variables with a normal distribution. The Mann–Whitney U test was used for continuous data that were not normally distributed. For categorical variables a chi-square or Fisher exact test was used. Multivariate logistic regression analysis was used to assay association of cytokines with studied groups in the presence of confounders such as age, sex, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, smoking, body mass index (BMI), stent type, and drugs. P-value less than 0.05 was considered significant.

Results

Baseline characteristics of the population

The characteristics of the individuals in the NISR and ISR groups are shown in Table 1. A total of 244 patients (71 female and 172 male) were enrolled. The mean age in the NISR and ISR groups were 62.47±9.2 and 59.49±8.48 years, respectively (p=0.017).

Association between stent type and DM with restenosis

The frequency of individuals with stent types in the NISR and ISR groups were significantly different as shown in Table 1. In particular 60% participants with a bare metal stent and 63.5% participants with a drug eluting stent were placed into the ISR and NISR groups, respectively (p=0.008). Moreover, there was a significant association between the ISR group and DM, so that 55.1% participants with DM were placed into the ISR group (p<0.001).

Table 1. Baseline characteristics in study groups.

Variables		NISR (165)	ISR (79)	*P value*
Age (y)		62.47±9.2	59.49±8.48	**0.017**
Sex (n%)	**Male**	113(68.5%)	59(75.6%)	0.160
	Female	52(31.5%)	19(24.4%)	
Smoking (n%)		29(18.0%)	9(11.7%)	0.169
HTN (n%)		105 (64.0%)	42(53.8%)	0.085
DM (n%)		50(30.9%)	43(55.1%)	**<0.001**
Dyslipidemia (n%)		153(94.4%)	75(96.2%)	0.569
Statin (n%)		151 (94.4%)	75 (98.7%)	0.624
Aspirin (n%)		152(95.0%)	74(97.4%)	0.131
Clopidogrel (n%)		142(89.3%)	68(89.5%)	0.415
NSAID		3(1.9%)	2(2.7%)	0.437
Corticosteroids		5(3.2%)	0(0.0%)	0.084
β blocker (n%)		27(16.4%)	14(17.7%)	0.461
ARB (n%)		50(30.3%)	20(25.3%)	0.258
ACE inhibitors (n%)		8(4.8%)	7(8.9%)	0.174
CCB (n%)		17(10.3%)	3(3.8%)	0.063
Insulin (n%)		18(10.9%)	7(8.9%)	0.402
Stent type (n%)	**Bare**	38(36.5%)	27(60.0%)	**0.008**
	Drug-eluting	66(63.5%)	18(40.0%)	
De novo lesion*		103(65.2%)	13(52.0%)	0.145
Duration between two angiography (months)		5 (2-8)	1 (1-2)	**<0.001**
BMI (n%)	**Normal**	64(42.4%)	24(33.3%)	0.350
	Overweight	66(43.7%)	34(47.2%)	
	Obese	21(13.9%)	14(19.4%)	
%LVEF(Mean±SD)		51.39±10.48	52.17±8.00	0.650
SBP (Mean±SD)		124.79±16.80	123.57±13.03	0.617
DBP (Mean±SD)		77.28±8.99	78.39±7.46	0.407

Normally distributed, abnormal distributed and categorical variables are reported as mean ± standard deviation (SD), median (IQR) and frequencies (percentages), respectively. A Student's T and chi-square test or Fisher exact were applied.
* Coronary obstruction more than 50% somewhere other than the stent
Abbreviations: SBP: systolic blood pressure; **DBP:** diastolic blood pressure, **LVEF:** left ventricular ejection fraction **CCB:** calcium channel blocker, **ACE inhibitors:** Angiotensin-converting enzyme inhibitors , **NSAID:** Non-steroidal anti-inflammatory drugs, **DM:** Diabetes mellitus, **HTN:** Hypertension.

Association between cytokines and restenosis

The serum cytokines in the ISR and NISR groups are shown in Table 2. The effect of confounding factors including age, DM, stent type and duration between two angiography were considered using multivariate regression analysis. The results showed that before and after correction, there was no significant difference in levels of pro/anti-inflammatory cytokines and growth factors between the two groups (p>0.05).

Highlights

- Occurrence of ISR was positively associated with age and duration between the two angiographies.
- Patients with the history of diabetes mellitus and previous bare stent implementation into coronary arteries were more susceptible to ISR.
- Serum cytokines levels including IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, EGF, and VEGF were not associated with ISR occurrence later than 1 month after stent implementation.

Discussion

According to literature, this is the first study evaluating the association between serum levels of pro/anti-inflammatory cytokines and growth factors with in-stent restenosis in 244 angiography patients who previously underwent coronary stent implantation in Iranian population. In particular 60% participants with a bare metal stent and 63.5% participants with a drug eluting stent were placed into the ISR and NISR groups, respectively. Moreover, there was a positive association between the ISR group and DM. Additionally, our results did not show significant association between serum levels of pro/anti-inflammatory cytokines and growth factors with in-stent restenosis (p>0.05).

Several studies reported association between cardiovascular events and atherosclerosis with inflammatory markers in CAD patients (19-21). In this regard we recently showed a significant association between serum hs-CRP level with ISR in a case-control study (22). In other study we reported a significant relationship between IL-1α, IL-8, MCP-1 and VEGF cytokines and CAD. Moreover, there was a significant difference between IL-4, IL-6 and EGF with the control, obstructive coronary artery disease and coronary artery bypass graft candidate groups (23).

Table 2. Association between cytokines and restenosis

Cytokines (pg/ml)*		NISR(165)	ISR(79)	Pvalue	Multivariate analysis**		
					OR	95%CI	P value
Pro-inflammatory	EGF	64.52(19.69-192.31)	44.43(10.42-189.87)	0.867	1.001	0.998-1.004	0.650
	IF-ɣ	0.00(0.00-0.00)	0.00(0.00-0.00)	0.114	0.522	0.244-1.117	0.094
	IL-1α	0.00(0.00-0.30)	0.00(0.00-0.00)	0.195	0.756	0.378-1.511	0.429
	IL-1β	0.00(0.00-1.05)	0.00(0.00-1.10)	0.545	0.906	0.621-1.322	0.610
	IL-2	0.00(0.00-0.00)	0.00(0.00-0.00)	0.098	0.868	0.674-1.119	0.274
	IL-6	1.83(0.90-4.02)	1.81(0.91-3.75)	0.939	1.004	0.983-1.025	0.717
	IL-8	9.34(4.30-30.37)	7.60(3.46-15.58)	0.259	0.998	0.994-1.002	0.305
	MCP-1	202.86(1.47-2.80)	183.10(134.65-243.55)	0.465	0.999	0.995-1.003	0.550
	TNF-α	2.37(1.86-3.09)	2.15(1.58-2.72)	0.836	1.007	0.980-1.034	0.629
	VEGF	133.72(46.34-292.82)	136.79(52.96-261.56)	0.639	1.001	0.999-1.003	0.274
Anti-inflammatory	IL-4	0.97(0.81-1.29)	1.01(0.85-1.29)	0.460	0.904	0.690-1.185	0.466
	IL-10	0.00(0-1.22)	0.00(0.00-1.12)	0.222	0.895	0.646-1.239	0.504

* Values are expressed as median and interquartile range for not normally distributed variables.
**Adjusted for age, DM, stent type and duration between to angiography.
Abbreviations; EGF: Endothelial growth factor, **IF- ɣ:** interferon-gama, **IL:** Interleukin, **MCP-1:** monocyte chemoattractant protein-1, **TNF-α :** Tumor necrosis factor alpha, **VEGF:** Vascular endothelial growth factor.

Several inflammatory factors including TNF-α and interleukins of IL-8, IL-12 and IL-1beta were evaluated in patient with CAD and it has been shown cytokines of IL-1β and TNF-α may be related to an induction of secondary cytokines including IL-8 and IL-6 (24, 25) (26, 27). Gostman et al., demonstrated in CAD patients, serum level of TNF-α is associated with the number of vessels involved (8). Molad et al., have reported the role of IL-8 as an inflammatory and angiogenic factor in the activation of neutrophils (28), that may be involved in the progression of atherosclerotic plaque (29).

Goldberg et al., showed high levels of IL-6 in patients with stable angina undergoing angiography that may involve in a systemic inflammation (30). Moreover, in the process of inflammation, the leukocytes and platelets-stimulated can lead to atherosclerosis and subsequently restenosis. Therefore, endothelial dysfunction is a key point in the initiation and development of CAD and ISR (31, 32).

Percutaneous coronary intervention (PCI) is the gold standard procedure to treat CAD while in-stent restenosis (ISR) is reported as a major limitation of this method (33, 34). CAD and ISR have different pathophysiological mechanisms while the presented arterial injury is triggered by stent placement in initiation of 2 process (35). Recently, determining the vascular pathology of restenosis has become a hot topic (36). However, inflammation has a key role in the initiation and progression of ISR and CAD processes (37). Other main factors involved in occurrence of ISR, including neo-intimal hyperplasia and the arterial endothelial injury, and endothelial proliferation (33, 34, 38) can be associated with high levels of inflammatory factors including cell adhesion molecules, TNF-α, MCP-1 and VEGF in PCI and restenosis process (37). Sukhija et al., did not find any significant relationship between serum TNF-α levels and restenosis in patients following angiography (24). Hojo et al., have reported the role of inflammatory cytokines in late restenosis of CAD. In this study, 40 patients with angina pectoris were divided in groups PCI, percutaneous atherectomy, and stent implantation. MCP-1 and M-CSF levels were assessed. The results showed that MCP-1 had no significant different 24h after PCI but M-CSF showed a significant higher plasma levels in patients with late restenosis 24 h after PCI (39).

Our results showed that before and after correction for confounding factors, there was no significant difference in levels of pro/anti-inflammatory cytokines between the ISR and NISR groups ($p>0.05$). Cipollone et al., have investigated inflammatory cytokines (e.g., MCP-1) as possible mediators of atherosclerotic process involved in ISR after PCI in 50 patients through a follow-up study (cytokines were measured before and 1, 5, 15, and 180 days after PCI). Angiography was repeated to diagnose ISR after 6 months. This study showed that plasma MCP-1 concentration has a main role in restenosis after PCI (40). Specifically, high concentration of MCP-1 chemokine could be associated with restenosis ($P=0.0001$), while RANTES and interleukin-8 chemokines had not significant differ between the restenosis and non-restenosis groups after PCI (40).

In regard with VEGF, our results were in accordance with results of Boldt et al., which did not show statistically significant association between ISR, NISR, lone patients with paroxysmal atrial fibrillation and lone chronic atrial fibrillation groups (41).

Limitations

The major limitation of our study was the measurement of cytokines for only one time. If we could provide a serial measurement of these 12 cytokines we could observe more practical results. Moreover, due to the decreased incidence of ISR because of widespread usage of coronary drug stents, the sample size of our study was limited, so subgroup analysis on DM or stent type was not applicable. Considering this limitation, we used multivariate logistic regression and adjust our analysis for these confounding factors.

Conclusion

We found that ISR was significantly related to DM and type of stent which have been previously shown to be strongly associated with ISR in several studies. Regard to pro-inflammatory and anti-inflammatory serum cytokines, we did not observe any significant difference between NISR and ISR groups. It

seems that inflammatory cytokines play a role in acute in-stent thrombosis in less than 1 month from stent implantation. For understanding the role of cytokines in ISR, it should be better to firstly design the study on a larger sample size and secondly limit the time of ISR occurrence to 1 month.

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