The Role of Interleukin-8 in Restenosis after Coronary Stent Implantation

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Abstract:

Background: In-stent restenosis (ISR) is a serious complication of percutaneous coronary intervention (PCI) with stent implantation. Variable factors may interact in the process of ISR. Immuno-inflammatory activity mediated by different cytokines could have a role in the ISR. Among these could be the chemokine, interleukin-(IL-8).

Aim of the Study: To assess the role of serum level of interleukin-8 in the process of ISR.

Patients & Methods: Forty patients with ISR (diagnosed by coronary angiography) within six months after coronary stenting. Patient control group enrolled 30 subjects who had had coronary stenting with no evidence (by angiography) of ISR .The third group composed of 20 healthy controls.

Results &Conclusion: Patients with ISR were mainly above the age of 50 years (62.5%) with male predominance (70%).Interleukin-8 was below detectable level (cut off value=553 pg/ml) in almost all cases with ISR with only 10% of the cases with ISR occur in the outer line values (outside usual range).

There was no significant difference in the frequency of detectable IL-8 levels between ISR patients and patient control group (P=0.284), neither between ISR patients and healthy controls (P=0.143).

In conclusion, the link between IL-8 and ISR was not found in this study.

Key words: Interleukin-8, Restenosis, Coronary stents.

Introduction:

The event of angiographic restenosis in the several months after initially successful PCI, although reduced in incidence with the development of stents, it still creates great impact on clinical and socioeconomic outcome [1].

The pathogenesis of ISR is mainly due to neointimal hyperplasia which is composed primarily from excessive proliferation of smooth muscle cells, extracellular matrix and inflammatory cells through the stent due to chronic irritation by a foreign body granulomatous reaction [2].

The process of ISR is associated with significant immuno-inflammatory activity. This can be assessed by examining the extent of circulating plasma levels of inflammatory markers such as; acute phase proteins (mainly C-reactive protein and serum amyloid A), cytokines, and anti endothelial cytoplasmic antibodies (AECA) [3].

Inflammatory cytokines had been proved few years ago to act effectively in mediating inflammatory/proliferative responses in atherosclerosis [4].The effective role of cytokines in the pathogenesis of ISR had been established recently. These include: IL-1 alpha, IL-1 beta, IL-6, G-CSF, TNF-alpha, INF-gamma, were all found to be increased in the follow-up period among patients developed restenosis [5].

Chemokines (chemotactic cytokines) are group of cytokines that are produced by various cells in area of damage and work to attract either macrophages or neutrophils to the site of initial inflammation. Chemokines are classified either as alpha or beta groups on bases of chemical and functional differences. Alpha chemokines attract neutrophils and are produced by activated mononuclear cells. Interleukin-8 is a very important member of this group [6]. Beta chemokines include RANTES

(Regulated upon Activation, Normal T Expressed and Secreted) and MCP-1 (Macrophage Chemoattractant Protien-1) which attract monocytes, T-cells and B- cells [7].

In the last few years, chemokines and their receptors found to play an effective role in the development of vascular diseases including restenosis [8].The role of IL-8 in vascular diseases that it may contribute to plaque formation (via its angiogenic properties) in human coronary atherosclerosis which is usually associated with increased vasa vasorum in the adventitia and within the plaque [9]. However, the contribution of IL-8 in the pathogenesis of ISR stills a matter of controversy.

This study is an attempt to assess if IL-8 had any role in the serious problem of ISR.

Patients & Methods:

This study was conducted on the following groups in the period between January and April 2004. The groups were matched for age and sex.

Patients Study Group: includes 40 patients with coronary artery disease admitted to the Iraqi Center for Heart Diseases in the Specialized Surgery Hospital. These patients had been angiographically diagnosed to have ISR within 6 months after coronary stent implantation.

Patients Control Group: This includes thirty patients from the same center who were subjected for angioplasty with stent implantation several months ago. They were proved to have patent stents and no evidence of ISR by repeat angiography.

Healthy Control Group: Twenty healthy volunteers were enrolled in this study so as to compare the general level of the parameters involved in this study.

All individuals were subjected to detailed questionnaire. Further information regarding procedural details was recorded from catheterization lab reports of each patient.

For each individual, Interleukin-8 level was assessed in the serum by direct immune enzymatic assay using CELL COM IM 2237 with two immunological steps (sandwich type).

Statistical Analysis: The statistical significance of difference between 2 groups was assessed by Chi square test or by Fischer's exact test when the criteria for valid Chi square test are not fulfilled (in case of small expected frequencies). A P-value of less than 0.05 was designated as statistically significant.

Results:

Distribution of patients with ISR by age and sex in comparison with control groups revealed that higher frequency of ISR was in 50-59 years age group with male predominance (male to female ratio 2.3:1). This is shown in table 1.

The frequency distribution of different IL-8 concentration in ISR patients revealed that the majority of these patients had IL-8 concentrations ranging between 225 and 718 pgm/ml which are almost entirely below the cutoff value (<553 pg/ml). It showed small heterogeneity in the undetectable range. There was a rare occurrence of an outer line (outside usual range) value in the positive extreme, 4 samples had values of 580, 585, 585, 718 pg/ml consequently. This is shown in figure 1.

Table-1: Age and sex distribution of the studied groups.

Age groups (years)	ISR patients **No. (%)**	control patients **No. (%)**	healthy control **No. (%)**
<40	4 (10%)	2(6.7%)	3(15%)
40-49	11(27.5%)	3(10%)	5(25%)
50-59	18(45%)	10(33.3%)	6(30%)
60-69	2(5%)	13(43.3%)	4(20%)
70+	5(12.5%)	2(6.7%)	2(10%)
Sex			
Male	28(70%)	21(70%)	14(70%)
Female	12 (30%)	9 (30%)	6 (30%)
Total	40(100%)	30(100%)	20(100%)

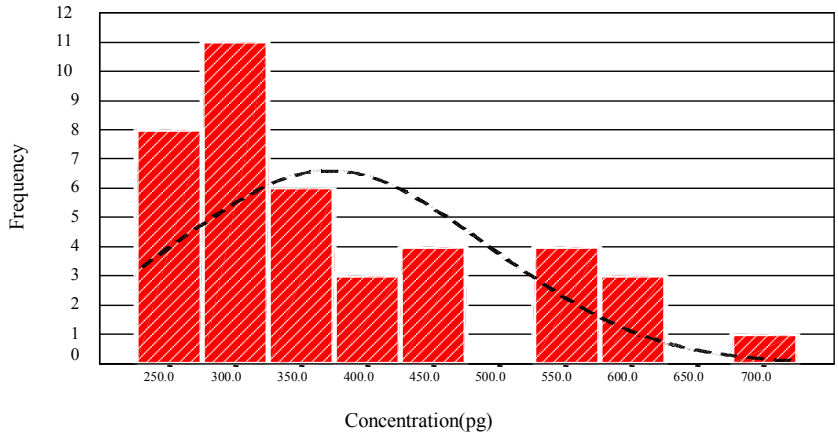

Figure –1: distribution of IL-8 concentration (pg/ml) in ISR patients [total no. 40]

In patients with ISR, Il-8 was detectable (above cutoff value) 4 patients (10%), compared with 1 patient (3.3%) of the control group. The difference was not statistically significant. IL-8 was not detected in any of the healthy group. These finding are demonstrated by table 2 and figure 2.

Regarding age and sex: IL-8 was detected in 3 different age groups of ISR patients with no statistical difference. The patients with detectable IL-8 were all males as shown in table 3**.**

Table-2: Detection of IL-8 in the Study Groups (cut off=553pg/ml)

Study group	**N**	**%**
ISR patient (n=40)	4	10
Control pt.(n=30)	1	3.3
Healthy (n=20)	0	0

$P(x^2)$
ISR Patients X Control= 0.284/NS/
ISR Patients X Healthy= 0.143/NS/

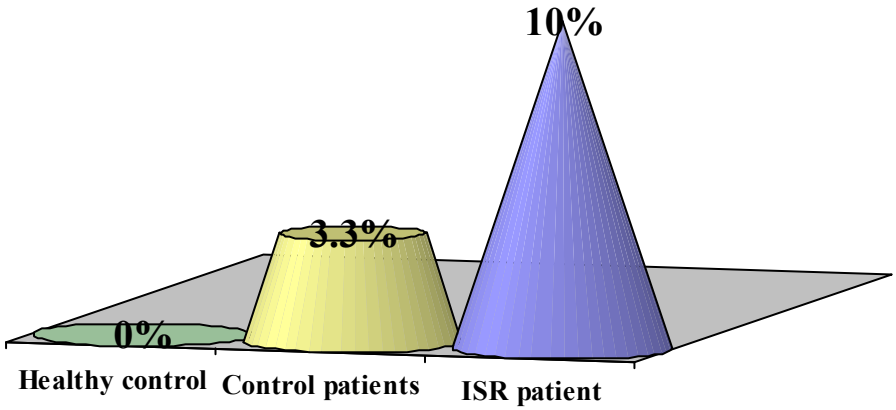

Figure-2 Cone chart comparing the frequency of detectable IL-8 in the three study groups.

Table-3: Detection of IL-8 in relation to age and sex in ISR patients.

Patients with detectable level of IL-8(cut off value=553 pg/ml)			
	N	**%**	**P-value**
1-**Age group(years)**			0.194
<40(n=4)	0	0	
40-49(n=11)	1	9	
50-59(n=18)	1	5.5	
60-69(n=2)	0	0	
70+(n=5)	2	40	
2-Sex			0.29
male(n=28)	4	14.3	
female(n=12)	0	0	

Discussion:

Rapid advances in molecular biology over the past decade have led to a new understanding of the etiology and pathogenesis of a number of vascular lesions including restenosis[10].

Patients with ISR were mainly above the age of 50 years (62.5%). This is consistent with an Iraqi study screened ISR in diabetic and non-diabetic patients[11] and with other abroad studies [12, 13]. They found that elderly patients have significantly higher rate of procedural complications and worse six months outcomes than younger patients. In-stent restenosis may affect both sexes. In the current study it is more common among males (70%) with male to female ratio 2.3:1. This is in agreement with other studies[11, 14] and most likely to be accepted due to the predominance of coronary artery disease in men[15] particularly this study involved wide range of age groups including pre and post menopausal females.

Detectable level of IL-8 (above cut off value) was observed in only 10% of patients with ISR at the time of diagnosis of this complication by angiography. No significant difference in frequency of detectable IL-8 level in the three groups of study. This finding coincides with those of Hojo et al 2001[16] and Cipollone et al 2001[6] who found that circulating level of IL-8 was not elevated in patients

after coronary angioplasty while MCP-1 and M-CSF (macrophage colony stimulating factor) usually play a pivotal role in the process of ISR by inducing macrophage accumulation and activation. So that neointimal proliferation usually occurs in association with macrophage accumulation and extensive revascularization, suggesting a role for organization of mural thrombus [17].

In conclusion the link between IL-8 (alpha chemokines) and the process of ISR was not present according to the study. Further studies need to find if any significant role of beta chemokines in inducing inflammation associated with the process of ISR.

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