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RESEARCH PAPER

Study of Interleukin 6 as marker of inflammation and a predictor of in-hospital complications in patients with acute coronary syndrome

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Abstract

Background: Although abnormal fatty deposits of infected arterial plaque play a major role in the formation of atherosclerotic plaque, activation of inflammatory cells plays a major role in the instability of the plaque and the cause of acute coronary syndrome. The aim of this study was to measure the level of interleukin-6 and to study its association with complications that occur in hospital in patients with acute coronary syndrome.

Method: One hundred and twenty-five patients with acute coronary syndrome and 120 healthy individuals as a control group were included in this study. According to ECG and serum troponin changes, the patient group was classified into three ST-elevated myocardial infarction, ST non-elevated myocardial infarction and unstable angina. Sandwich ELISA was used by commercial groups (LEGAND MAX TM) for the IL-6 assay.

Result: This study shows significantly significant differences in the level of IL-6 in patients with acute coronary syndrome (73.37 pg / dL) compared to the control group (9.47 pg / dL) (P value 0.001). There were no significant differences at the level of IL-6 in patients with acute coronary syndrome and conventional risk factors (P. value <0.05). There were significant differences in the level of IL-6 in all forms of ACS. (P. value 0.001). And those patients who had complications in hospital had a higher IL-6 level (92.89 Pg / dl) than those without complications (68.83 Pg / dl) P. value (0.012).

Conclusion: This study indicated that IL-6 was significantly elevated in ACS patients and may be a good predictor not only of acute coronary event but also disease severity and a prediction of complications

Keywords: ACS, interleukin-6, STEMI, NSTEMI, unstable angina, complications

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Introduction

Cardiovascular disease is now the most common cause of death worldwide and among cardiovascular deaths; The vast majority are attributed to acute coronary syndrome (ACS) [1]. The World Health Organization (WHO) reports that ischemic heart disease (IHD) has been the leading cause of death globally in the past 15 years. One in 7 deaths has been reported to be caused by ischemic heart disease globally, and it has been estimated to account for 40% of deaths in 2030 for people over 65 years of age [2].

Although it was previously considered a fat storage disease, major developments in basic and experimental science have elucidated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherosclerosis. [3]. Stable plaques may regress, remain fixed, or grow slowly over several

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decades until they cause narrowing or blockage. Whereas unstable plaques are prone to spontaneous erosion, fissure, or rupture, causing acute thrombosis, embolism and infarction long before they cause significant stenosis in hemodynamics [4]. The stability of plaque depends on multiple factors, including: plaque formation, wall stress (cap fatigue). Size and location of the core and configuration of the plaque in relation to blood flow [5]. Rupture of plaques predisposes to thrombosis, macrophage death by apoptosis of the necrotic core of plaque [6]. Fissuring or rupture of these plaques and consequent exposure of core constituents such as lipid, smooth muscle, and foam cells leads to the local generation of thrombin and deposition of fibrin. This in turn promotes platelet aggregation and adhesion and the formation of intracoronary thrombus [7].

Interleukin-6 (IL-6) is a cytokine produced by different types of cells. It exerts many of its activities by interacting with specific receptors that are expressed on the surface of target cells. The biological activities of IL-6 include stimulation of B and T cell growth and differentiation, and production of acute phase proteins [8]. Therefore, this study aimed to measure the level of interleukin-6 in ACS patients and to study their role as an early marker of inflammation in ACS as well as to understand whether interleukin-6 differs in a different form of ACS and its association with the hospital ACS complications.

Methods

One hundred twenty-five patients with ACS and 120 persons as control group were included in this study for the period between March 2019 to January 2020, their age ranged from 31 to 95 with mean (58.72 ± 12.32 SD). An ethical approval was getting from the committee board of the Iraqi health and higher education authority before start collection the samples. Out of 125 patients with ACS 68 (54.4 %) were males and 57(45.6%) were females. Review of history was taken; Physical examinations were done. Routine blood count and serum biochemistry were requested.

Twelve leads Electrocardiography was done and review by expert cardiologists. According to electrocardiography changes and serum troponin, patients' group was sub - classified to three groups ST elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI) and unstable angina.

Five milliliter of venous blood samples were obtained from all patients at time of admission to CCU at Albasrah and Alsader teaching hospital and prepared for IL-6 level assay.

Sandwich ELISA was used by commercial kits (LEGAND MAX TM) for IL-6 assay. The procedure was done according to the kit manufacturing instruction company and the ELISA test was done at the Albian Laboratory Center which is located in Basrah city.

Statistical analysis

Data were analyzed statistically using SPSS version 20. Means and standard deviation were used to describe the data distribution. Analysis of (ANOVA or F-test) was used to compare more than two means, when analysis is important, post-hoc test is used to determine the significance of group analysis. An independent t-test is used to determine the significance between the means of two groups. The test is considered significant if the P-value is less than 0.05.

Results

This study showed that STEMI was the commonest form of ACS observed in 75(60%) of patients (Figure 1, Table 1).

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Table 1: Frequency of patients among different form of ACS

TYPES OF ACS	NO. OF PATIENTS (%)
STEMI	75 (60)
NSTEMI	21 (16.8)
UA	29 (23.2)
Total	125(100)

It shows statistically highly significant differences in the level of IL-6 in patients with ACS (73.37 pg/dl) versus (9.47pg/dl) in control group (P. value 0.001) (Table 2).

Table 2: The mean of IL-6 and TNF-α in patients and control groups

	ACS	CONTROL	P. VALUE
Average IL-6	73.37	9.47	0.001
Average TNF-α	27.49	10.62	0.001

It also demonstrated that there were no statistically significant differences between the traditional risk factors that were studied and the level of IL-6 in patient with ACS (Table 3).

Table 3: Relationship of IL-6 with some risk factors

		NO. OF PTS. (%)	IL-6	P VALUE
Gender	Male	68 (54.4)	84.27	0.33
	Female	57 (45.6)	71.93	
Smoker	Yes	39 (31.2)	95.34	0.110
	No	67 (53.6)	67.19	
	X-smoker	19 (15.2)	85.75	
Obesity	Yes	20 (16%)	76.17	0.86
	No	105 (84)	79.03	
Hypertension	Yes	72 (57.6)	82.26	0.105
	No	53 (42.2)	90.08	
Diabetes	Yes	65 (52)	75.12	0.755
	No	60 (48)	78.76	
Family history	Yes	28 (23.2)	61.14	0.115

Highly significant differences in the level of IL-6 among different type of ACS (STEMI 95.576), (NSTEMI 60.669), unstable angina (42.103) and control group (9.105) has been shown (P. value 0.001) in (Table 4).

Table 4: The mean of IL-6 among different type of ACS

	NO. OF PTS.	MEAN OF IL-6	SD	P VALUE
STEMI	75	95.57	77.07	0.001*
NSTEMI	21	60.66	48.97	
UNSTABLE ANGINA	29	42.10	29	
CONTROL	120	9.10	6.52	

Interestingly the interleukin -6 was the highest in STEMI group among the different form of ACS (NSTEMI and unstable angina) (Table 4). These differences were statistically highly significant. (P. value between STEMI and NSTEMI groups (0.013) and between STEMI and UA groups (0.001). However, there was no significant difference in the level of IL-6 between NSTEMI and UA groups (0.497).
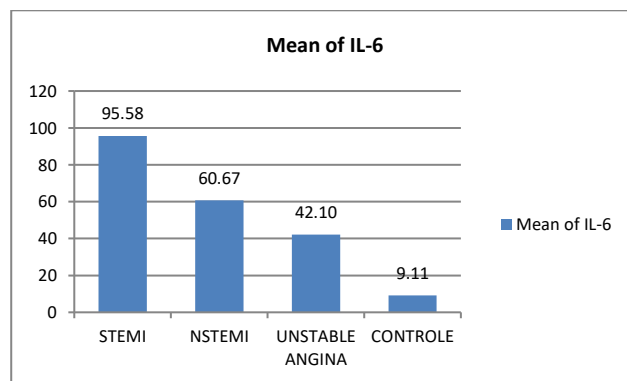

Figure 1 The mean level of IL-6 among different form of ACS and control groups

Another interesting finding this study reported there were no statistically significant differences on the effect of gender in the level of IL-6 among different form of ACS (P value 0.189) (Figure 2).

Thirty-six (28.8%) patients had in-hospital complications. There were significant differences in the mean IL-6 level between patients with complications (92.895 pg / dL) and those without complications (68.835 pg/ dL) (P. value 0.012) (Table 5). Heart failure was the most common complication reported in this study, but the mean level of IL-6 did not differ significantly from a patient with heart failure from patients with other complications (e.g., arrhythmias, post MI angina, and hypotension), nor in patients with heart failure plus other complications (mean levels were 93.24, 57.29, 122.37 pg / dL, respectively) (P-value 0.312) (Figure 3)

Table 5: The mean level of IL-6 between patients with complications and patients without complications

	NO. OF PATIENTS (%)	MEAN OF IL-6 (PG/DL)	SD OF IL-6	P. VALUE
Complications	36(28.8)	92.89	83.16	0.012
Without complication	89(71.2)	68.83	58.99	

Discussion:

The roles of pro-inflammatory and anti- inflammatory cytokine in pathogenesis of the disease get great consideration in recent studies. A balance between pro-inflammatory and anti-inflammatory cytokines is necessary to maintain health [9].

The roles of IL-6 which has both the pro-inflammatory and an anti-inflammatory effect [10], in ACS was the focus of our interest in this study.

This study shows statistically highly significant increase in the level of IL-6 in patient with ACS (73.37pg/dl) as compared with control group (9.47 pg/dl) (p value 0.001). This result was in consistent with other studies [11-14].

Simon et al. were administered that not only increase level of pro-inflammatory cytokine concentrations were important but also decrease level of anti-inflammatory cytokine concentrations were important in patients with ACS as well [15].

On the other hand, Frangogiannis et al. were reported that Pro-inflammatory cytokines are also involved in reperfusion injury, repair processes and scar tissue formation after myocardial infarction [16].

There were no statistically significant associations at the level of IL-6 with age of patients or their sex. These were with agreement with other studies [14, 17].

Mowafy et al. showed no significant differences regarding gender but there were significant differences shown with age in Egyptian patients. The explanation for these differences might be due to the including of younger populations whom were enrolled in their study despite similar sample size. (Their age ranges from 18–40 years only) [18].

There was no significant association between some of traditional risk factors (smoking, family history, obesity, hypertension and diabetes,) with level of IL-6 (p. value 0.110, 0.115, 0.86, 0.105, 0.755 respectively) (Table 3). These findings were in consistent with other studies [10,18, 19].

A statistically significant differences in IL-6 level in all forms of ACS (STEMI, NSTEMI and UA) in comparison with control group P. value (0.001,0.001,0.04 respectively) were reported in this study and that were come in agreements with other researches finding [20-23].

Swirski administered that cells death of lipid-laden foam cells lead to formation of large necrotic lipid core and release of IL-6 and other cytokines, which is implicated in the destruction of its fibrous cap and plaque instability that leads to development of ACS [24].

This study shows that the IL-6 was higher in STEMI group than NSTEMI and UA groups (p. values 0.013, 0.001 respectively). This was in the direction with other studies [18, 25]. This might be explained by the fact that in STEMI the pathology was more advance and usually there is transmural necrosis of myocardium and this might reflect that IL-6 level is good indicator of degree of injury to tissue and to the severity of ACS.

IL – 6 has been shown to be more sensitive and specific as compared to CRP in vascular inflammation and elevated IL -6 levels correlated with increased risk of future MI [26]. It has been proposed that IL-6 cause plaque instability by modifying TNF-alpha and monocyte chemoattractant protein-1(MCP-1) [26]. Moreover, Ridker showed that healthy individuals
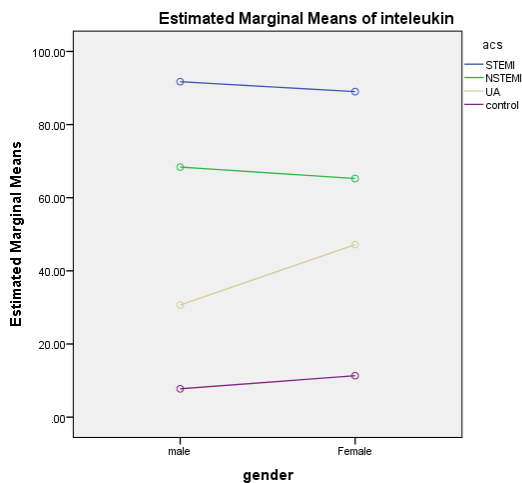

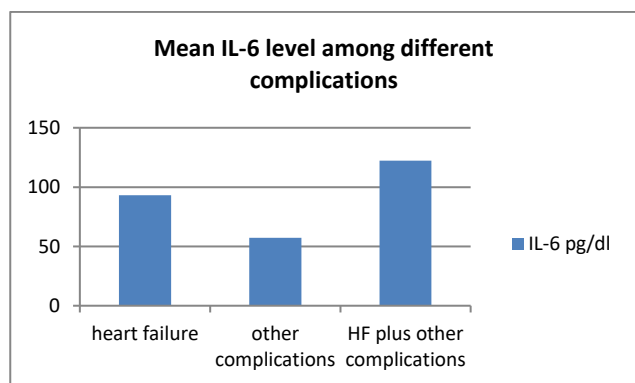**Figure 2 The mean of IL_6 among different form of ACS and control groups**

Figure 3 The mean IL-6 level among different complications

with higher interleukins had a higher chance to have future MI [26]. Thirty-six (28.8%) patients enrolled in this study had complications. There were statistically significant differences in the mean level of IL-6 between patients with complications (92.895 pg/dl,) and those without complications (68.835pg/dl). (P. value 0.012), this was accordance with other studies [14, 27].

Gotsman et al [14] and Ridker et al [26] were administered that an increase in the level of IL-6 in a patient with ACS was not only associated with an increase in complications but also with disease severity and the number of severely affected vessels (> 50% -70% stenosis on angiogram).

Due to the small sample size of patients with complications, this study was unable to uncover statistical analysis with different forms of complications and recommended further investigation to give a complete idea of the relationship. One limitation of this study was the association between the type of complication and the level of interleukin-6; Although Figure 3 shows a higher level of interleukin-6 in the patient with heart failure, this was not statistically significant. Another study with a larger sample size is highly recommended.

Conclusion:

IL-6 level was markedly elevated in patients with ACS and it might be good indicator not only for acute coronary event but also for severity of the disease and predictor for probability of development of complications in patients with coronary artery disease.

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