Evaluation of IL18 in acute coronary syndrome patients and its relation to diabetes

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Abstract: To assess interlukein 18 in patients with acute coronary syndrome (ACS) with and without diabetes and to detect its relation to lipid profile. **Patients and Methods:** The study included 40 ACS patients (20 patients had type 2 diabetes mellitus) and 15 age and sex matched as a control group. **Results:** Total cholesterol is significantly higher and HDL-c is significantly lower in diabetic patients with ACS than the other 2 groups. IL18 is significantly higher is diabetic patients with ACS followed by non diabetic patients with ACS than the control group. No significant correlation was found between IL8 and blood glucose level or lipid profile in the 3 groups. **Conclusion:** IL18 is an inflammatory marker in patients with ACS and diabetes. No relation between IL18 and lipid profile. In addition, IL-18 levels were associated with traditional risk factors such as diabetes mellitus.
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Keywords: IL18; coronary syndrome; diabetes.

1. Introduction

Chronic inflammation causes atherosclerosis and is also involved in atherosclerotic plaque disruption and thrombosis, and may greatly influence the occurrence of acute ischemic syndrome (1).

Interleukin (IL)-18, originally termed interferon (IFN)-γ-inducing factor, is a newly discovered cytokine with pleiotropic activities extending from T-helper 1 cell (Th1) polarization of the immune response to a proinflammatory activity. The multifunctional properties of IL-18 production in numerous diseases, such as infections, several types of cancer, and in-inflammatory and autoimmune diseases, reflect an inappropriate immune response (2).

IL-18 is found in the unstable atherosclerotic plaque, in adipose tissue and in muscle tissue, and is subjected to several regulatory steps including cleavage by caspase-1, inactivation by IL-18 binding protein and the influence of other cytokines in modulating its interaction with the IL-18 receptor (3). A recent study showed significant expression of IL-18 in human carotid atherosclerotic plaques (4). Increasing plasma levels of IL-18 in patients with acute coronary syndrome were reported to be associated with increased mortality (5). Moreover, the serum IL-18 level was identified as a strong independent predictor of death from cardiovascular causes in patients with coronary artery disease (6). However, the effects of IL-18 on the production of other cytokines in coronary artery disease are still unknown.

The objectives of the present study were to analyze the serum levels of IL-18 in patients with acute coronary syndrome and to compare possible variations of serum levels between the groups according to the presence of diabetes.

2. Materials and Methods

Patients:

The study population consisted of 40 patients with acute coronary syndrome admitted to ICU. ACS was diagnosed by ; persistent typical chest pain (precordial radiating to the left shoulder and back) on admission, ECG changes, ST segment depression and / or T wave changes and elevated cardiac enzymes (CK, MB, LDH and Troponin),non-ST segment elevation myocardial infarction, or unstable angina. Diabetes was present among 20 patients only and 15 age and sex matched healthy persons served as a control group.

Exclusion criteria:

Pregnancy; Class III or IV congestive heart failure; Valvular heart disease; History of acute myocardial infarction in the preceding four weeks; Atrial fibrillation; Any ECG abnormality that could affect the analysis of the ST-segment; History of surgery or trauma in the preceding four weeks; History of chronic or acute inflammatory disease and History of malignancies.

Methods:

The study was done after obtaining approval from the local institutional review board and human subject's protection. Written informed consent was obtained from all patients.

Patients were subjected to ECG recording on admission and every 6 hours during the first 24 hr. Also serial cardiac enzymes were done on admission and every 8 hr during the first 24 hr.

Venous blood samples (10 ml) were drawn in the morning after an overnight fasting from each subject. The venous blood sample was divided into three test tubes. 1 ml was added to a mixture of potassium oxalate and sodium fluoride (for plasma glucose estimation by oxidase/peroxidase kit (7), 2 ml was added to EDTA powder (whole blood to estimate HbA1c by cationic exchange resin(8) and the remaining 7 ml were allowed to clot at room temperature then centrifuged at 1000 rpm for 15 minutes. Serum was separated and divided into aliquots then frozen at -70 ^{0}C till the time of assay. The serum samples were used to estimate the Interleukin 18: by a solid phase enzyme linked immunosorbent assay (ELISA) Kit (9).

Plasma concentrations of cholesterol and triglycerides, LDL and HDL were determined by quantitative colorimetric kit.

Statistical Methods:

Statistical Package for social science (SPSS) version 9.0 was used for analysis of data (Chicago, Illinois, USA). Non Parametric test (Mann Whitney U) test was done for analysis of 2 quantitative data, as data was not symmetrically distributed. One way ANOVA was used for comparison of the 3 groups followed by post hocc test (LSD) for detection of significance. Pearson's correlation was also done.

3. Results:

The study included 40 patients with ACS their mean age was 55.5 ± 3.2 yrs (54 – 72 yrs). Twenty patients did not have diabetes, their mean age was 64.5 ± 2.6 yrs (54 – 70 yrs), 20 diabetic patients, their mean age was 65.8 ± 3.3 yrs (60 – 72 yrs) and 15 age and sex matched as a control group, their mean age was 64.2 ± 3.1 yrs(55 – 68 yrs).

Table 1 : Comparison between laboratory data of patients with acute coronary syndrome and controls included in the study

Variables	Patients with acute coronary syndrome Mean ± SD N = 40	Controls Mean ± SD N = 15	P –value
Fasting blood glucose (mg \ dl)	148.0 ± 82.7 (73 – 360)	89.7 ± 9.4 (70.0 – 105.0)	0.01*
Total cholesterol (mg\dl)	194.7 ± 36.4 (109 – 290)	185.6 ± 9.8 (166.0 – 200.0)	0.4
Triglyceride (mg\dl)	159.6 ± 32.8 (76 – 225)	169.6 ± 4.9 (159.0 – 177.0)	0.2
HDL-c (mg\dl)	44.7 ± 13.9 (28 – 93)	47.4 ± 5.4 (40.0 – 58.0)	0.5
LDL –c (mg\dl)	147.0 ± 12.7 (122 – 190)	148.1 ± 7.3 (136.0 – 159.0)	0.8
IL18	509.1 ± 237.0 (220 -950)	69.2 ± 7.8 (55.6 – 80.5)	0.0001*

Table 2: Correlation between IL 18 of patients with acute coronary syndrome included in the study with other laboratory data

Variables	Patients with Acute coronary syndrome	
	R	P- value
Fasting blood glucose (mg \ dl)	- o.o2	0.9
Total cholesterol (mg\dl)	- 0.1	0.8
Triglyceride (mg\dl)	-0.5	0.07
HDL-c (mg\dl)	0.2	0.4
LDL –c (mg\dl)	0.01	1.0
HbA1 (%)	0.5	0.04*

Table 3 : Comparison between laboratory data of diabetic and non diabetic patients with acute coronary syndrome and controls included in the study

Variables	Diabetic with acute coronary syndrome Mean ± SD N = 20	Non Diabetic with acute coronary syndrome Mean ± SD N = 20	Controls Mean ± SD N = 15	P –value
Fasting blood glucose (mg \ dl)	209.9 ± 76.7[a] (118.0 – 360.0)	86.1 ± 8.0[b] (73.0 – 98.0)	89.7 ± 9.4[b] (70.0 – 105.0)	0.0001*
Total cholesterol (mg\dl)	211.2 ± 41.3[a] (143.0 – 290.0)	178.2 ± 21.4[b] (109.0 – 204.0)	185.6 ± 9.8[b] (166.0 – 200.0)	0.005*
Triglyceride (mg\dl)	162.1 ± 38.1 (83.0 – 225.0)	157.0 ± 27.6 (76.0 – 185.0)	169.6 ± 4.9 (159.0 – 177.0)	0.5
HDL-c (mg\dl)	37.1 ± 6.6[a] (28.0 – 52.0)	52.3 ± 15.3[b] (42.0 – 93.0)	47.4 ± 5.4[b] (40.0 – 58.0)	0.001*
LDL –c (mg\dl)	149.6 ± 15.9 (122.0 – 190.0)	144.3 ± 8.1 (135.0 – 158.0)	148.1 ± 7.3 (136.0 – 159.0)	0.4
IL18	662.3 ± 245.1[a] (230.0 – 950.0)	355.9 ± 77.2[b] (220.0 – 500.0)	69.2 ± 7.8[c] (55.6 – 80.5)	0.0001*

Different symbol indicates significance.

Table 4: Correlation between IL 18 of diabetic and non diabetic patients with acute coronary syndrome and controls included in the study with other laboratory data

Variables	Diabetics with acute coronary syndrome		Non Diabetics with acute coronary syndrome		Controls	
	R	P- value	R	P- value	r	P- value
Fasting blood glucose (mg \ dl)	0.3	0.3	-0.2	0.6	- 0.02	0.9
Total cholesterol (mg\dl)	-0.4	0.2	0.1	0.8	0.5	0.07
Triglyceride (mg\dl)	-0.1	0.8	0.1	0.8	0.2	0.4
HDL-c (mg\dl)	-0.3	0.3	-0.4	0.1	0.01	1.0
LDL –c (mg\dl)	-0.03	0.9	-0.2	0.4	0.5	0.07

4. Discussion:

IL-18 is found in the unstable atherosclerotic plaque, in adipose tissue and in muscle tissue, and is subjected to several regulatory steps including cleavage by caspase-1, inactivation by IL-18 binding protein and the influence of other cytokines in modulating its interaction with the IL-18 receptor (3). Interleukin-18 (IL-18), a proinflammatory cytokine, has been associated with atherogenesis and plaque rupture in acute coronary syndrome (ACS). Recent studies suggest that IL-18 may have a long-term prognostic value (10)

In the current study, Patients with acute coronary syndrome had a significantly higher level of fasting blood glucose and IL 18 than controls (table 1).

According to a report that the focus of systemic inflammation in patients with unstable angina is the result of low-grade myocardial necrosis (11), circulating IL- 18 may also reflect the myocardial damage seen in patients with acute coronary syndrome. Thus, the effects of IL-18 on myocardial damage in ischemia are much less well understood. A recent study showed that the endogenous inhibitor of IL-18 and IL-18 binding protein modulates the development and stability of atherosclerosis in ApoE knockout mice (12).

Evidence from experimental studies has emerged that expression of IL-18 is intimately related to atherosclerotic plaque progression and vulnerability (13 -16). These results could be translated into the clinical setting, as shown in the AtheroGene Study, which suggested that the concentration of circulating IL-18 was one of the strongest predictors of future cardiovascular events in patients with stable and unstable angina (17).Also Furtado et al (10) concluded that Serum IL-18 levels in ACS patients were independent predictors of long-term cardiovascular events. These findings support the association between inflammation and prognosis of ACS patients, as well as the clinical impact of this biomarker

Additionally, Hartford et al (18) found that IL-18 levels were significantly related to cardiovascular mortality. IL-18 independently predicted CHF, MI, and cardiovascular death in both

the short and long term and concluded that the addition of the measurement of IL-18 to clinical variables improved the prediction of risk of cardiovascular mortality

Yamaoka-Tojo et al (19) demonstrated for the first time that measurement of IL-18 provides important information about the severity of myocardial damage in patients with acute coronary syndrome.

Mallat et al, (20), reported two potentially important findings, first, plasma concentrations of IL-18 are increased in patients with acute coronary syndromes with or without myocardial necrosis. Second, plasma concentrations of IL-18 correlate with the severity of myocardial dysfunction.

In the present study, IL 18 has a significant positive correlation with HbA1 in all patients with acute coronary syndrome (table 2). Also, IL18 shows a significant higher level in diabetic patients with ACS followed by non diabetic patients with ACS than the control group (table 3).

In accordance to these results Chazova et al (21) found that serum level of IL18 was increased in patients with type 2 diabetes mellitus and ACS and concluded that IL18, chronic hyperglycemia and depresssive disorders play an important role in development of latent inflammation of the vascular wall in patients with type 2 diabetes mellitus and ACS

Hyperglycemia itself, a characteristic of glucose intolerance, is related to the immediate synthesis of markers such as IL-6 and IL-18, with serum level variations positively correlated and with more significant increases in hyperglycemic spikes, a situation that is common in diabetic patients (22).

Since patients with diabetes comprise a significant part of the population with coronary artery disease (20-24%), the understanding of the inflammatory mechanisms in diabetes and also in insulin resistance is fundamental for a proper treatment (23).

Our study showed that, total cholesterol is significantly higher and HDL-c is significantly lower in diabetic patients with ACS than the other 2 groups (table 3). No significant correlation was found between IL18 and blood glucose level or lipid profile in the 3 groups (table 4).

In the contrary, Hulthe et al (24) reported that the plasma IL-18 concentration was associated with a range of traditional cardiovascular risk factors such as BMI, LDL- and HDL-cholesterol, triglyceride, insulin and proinsulin .

5. Conclussion:

Increased plasma IL-18 level is observed in patients with ACS and diabetes. In addition, IL-18 levels were higher in diabetic patients than nondiabetics. No correlation was found between IL18 and lipid profile.

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