

The Level of Tumor Necrosis Factor–Alpha in Patients with Acute Coronary Syndrome

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Abstract

Objectives: This study was used to measure the level of tumor necrosis factor-alpha in patients with acute coronary syndrome.

Method: A case control study was used; the level of tumor necrosis factor-alpha was measured in 39 patients with acute coronary syndrome (30 male, 9 female) & 20 (12 male, 8 female) control group; risk factors (smoking, hypertension, diabetes mellitus), duration of staying in cardiac care unit & complications (recurrent angina pain, hemodynamic, electrical) are also recorded.

Result: we were found significant increase in the level of tumor necrosis factor-alpha in all patients with acute coronary syndrome as compared with control group (P value < 0.01) the highest level of tumor necrosis factor-alpha are associated with myocardial infarction rather than unstable angina patients & also high rate of complications.

Conclusion: According to this study tumor necrosis factor-alpha was significantly increased in acute coronary syndrome & could be used for determining severity of the diseases in patients with acute coronary syndrome.

Keywords: Tumor necrosis factor-alpha, patients, acute coronary syndrome

Introduction

Atherosclerosis is currently one of the main causes of death; a great majority of deaths related to atherosclerosis occur due to acute complications, mainly based on plaque disruption.^{1,2} Inflammation is the most important mechanism of plaque disruption of which it is crucial to reveal the molecular mechanisms.^{3,4} Previously, the appearance of immune cells at the ischemic site of myocardial tissue was believed to be a response to tissue injury. Inflammatory processes are now recognized to play a central role in pathogenesis of atherosclerosis and its complications. A growing body of evidence suggests that acute coronary syndrome is associated with local and systemic activation of the immune system. Plasma levels of several inflammatory markers have been found to be associated with future cardiovascular risk in a variety of clinical settings. These markers include cell adhesion molecules, cytokines, pro-atherogenic enzymes and C-reactive protein.⁵ Recent studies suggest that markers of inflammation may reflect different aspects of the atherothrombotic process at different points in the continuum of acute coronary syndromes, Prediction of risk for developing coronary artery disease, and could correlate with severity and future risk for coronary artery disease.⁶ Inflammation markers such as C-reactive protein, fibrinogen and cytokines have been implicated in the development and progression of coronary artery disease.⁷⁻¹³ Tumor necrosis factor (TNF): It is lymphokines produced primarily by cells of the immune system, capable of causing in vivo hemorrhagic necrosis of certain tumor cells but not normal cells.¹⁴ They also destroy cells associated with the inflammatory response. They have been used as experimental anticancer agents but can also induce shock when bacterial endotoxins cause their release.¹⁵ *Tumor necrosis factors α* , formerly called cachectin, contains 157 amino acids and is produced by macrophages, eosinophils, and NK cells. *Tumor necrosis factor β* is lymphotoxin and contains 171 amino acids.¹⁶ Tumor necrosis factor (TNE, cachexin or cachectin) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that

stimulate the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by other cell types as well.¹⁷ The primary role of TNF is in the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, sepsis (through IL1 & IL6 production), cachexia, and inflammation and inhibit tumorit genesis and viral replication. Dysregulation of TNF production has been implicated in a variety of human diseases, including Alzheimer's disease, cancer, major depression, and inflammatory bowel disease.¹⁸ Tumor necrosis factor- α can be produced ectopically in the setting of malignancy and parallels parathyroid hormone both in causing secondary hypercalcemia and in the cancers with which excessive production is associated.¹⁹ The purpose of this research is to identify high-risk groups among patients admitted to the cardiac care unit by measuring their levels of tumor necrosis factor alpha (TNF-alpha) and assessing the use of this marker in predicting the prognosis of patients with coronary artery disease.

Methods

This study was conducted at Al-Kadhymia Teaching Hospital, the study groups included 59 persons; 39 patients with ACS (19 patients with acute myocardial infarction & 20 patients with unstable angina based on clinical, ECG & Echo finding) 9 females and 30 males; mean age (60 years) and 20 control group; 12 males & 8 females mean age (58 years). We excluded patients with clinical evidence of any infectious diseases, severe co morbid diseases like severe COPD, chronic renal failure & neoplastic diseases. All of the patients with ACS were hospitalized and their medications were initiated as appropriate. All patients received Aspirin, beta-blocker, weight-adjusted low molecular weight or unfractionated heparin and lipid lowering therapy. Blood samples were obtained from the patients with ACS (within a maximum 12 hr. after the onset of pain) to reveal biochemical parameters; Blood samples were centrifuged at 5000 rpm for 5 min and the collected serum samples were stored for a maximum time period of 1 month.

After taking the samples; the patients were followed up in the CCU throughout their admission period for occurrence of complications using clinical, ECG, radiological and echostudies & their complication were recorded. TNF-alpha kits were purchased from (Ray Biotech, INC, USA) and Bio-source (USA), and the results were interpreted according to the instructions given by the manufacturer.

Statistical Analysis

Comparisons between patients & control groups were performed using *T*-test *P*-value < 0.05 was considered statistically significant.

Results

39 patients with acute coronary syndrome were compared with control group (20 patients without history of coronary artery disease) as shown in Table 1. Patients with ACS have mean age 60 years (30 male, 9 female); 61% of them have history of hypertensive, 43% of them were diabetic, 59% were smokers. Control group have mean age 58 years (12 male, 8 female); 40% were hypertensive, 20% of them were diabetic, 60% of them were smokers. There is significant increase in the level of TNF-alpha in all patients included in the study groups (patients with ACS) & *P*-value < 0.01 as compared with control group. The highest levels of TNF-alpha were associated with acute MI as shown in Figure 1. The CAD complications encountered in the study were recurrent angina pain, hemodynamic complications like (hypotension, pulmonary edema), electrical abnormalities like (AF, 2d & 3d heart block) these complications were recorded in 43.5% of patients with ACS as shown in Figure 2. Rate of occurrence of these complications were associated with increase in the level of TNF-a as shown in Figure 3. None of above parameters age, gender, risk factors (hypertension, DM, smocking, lipid profile) was statistically different between study & control group as shown in Table 1.

Discussion

There are many studies support a role for inflammation in the pathogenesis of coronary atherosclerosis & unstable cardiac

Table 1. Characteristics of the patients & control groups & *P*-value

Patient criteria	Patient with ACS N (39)	Control group N (20)	<i>P</i> -value
Age	60 ± 10	58 ± 9	> 0.05
Gender	Male 30 Female 9	Male 12 Female 8	
Smoking	23 (59%)	12 (60%)	> 0.05
Hypertension	24 (61%)	8 (40%)	> 0.05
Diabetes mellitus	17 (43%)	4 (20%)	> 0.05
Serum cholesterol (mmol/l)	3.6 ± 0.9	3.3 ± 0.7	> 0.05
Duration of stay in CCU (days)	3.02 ± 0.9	0	
TNF-alpha level (Pg/ml)	6.77 ± 2.7	4.5 ± 0.5	< 0.01

The level of TNF in Acute myocardial infarction & Unstable angina & Control groups



Fig. 1 The level of TNF in Acute myocardial infarction Unstable angina & Control groups.

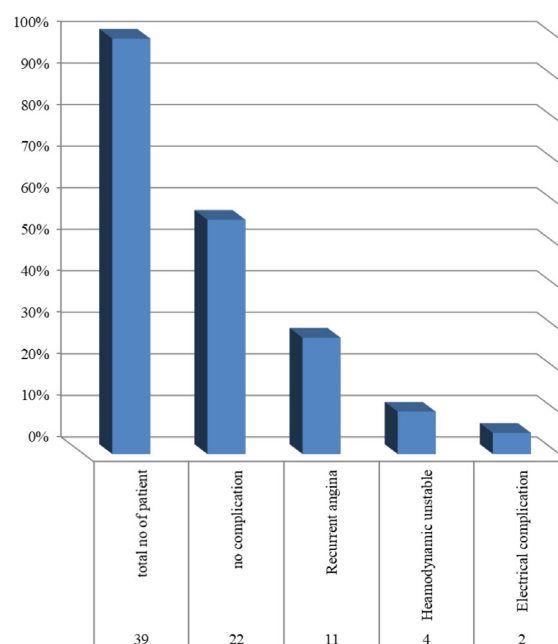


Fig. 2 (Types & frequencies of complications in patients with acute coronary syndrome).

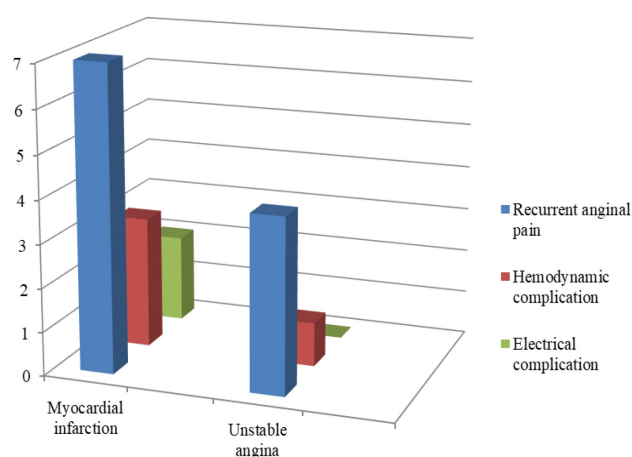


Fig. 3 (Types & frequencies of complications in patients with MI & UA in the patients groups).

syndromes; the pattern & magnitude of cytokines release at the site of tissue injury is considered to be a critical determinant of severity and duration of response.^{20,21} TNF-alpha plays a role in the processes of coagulation, ischemia and reperfusion

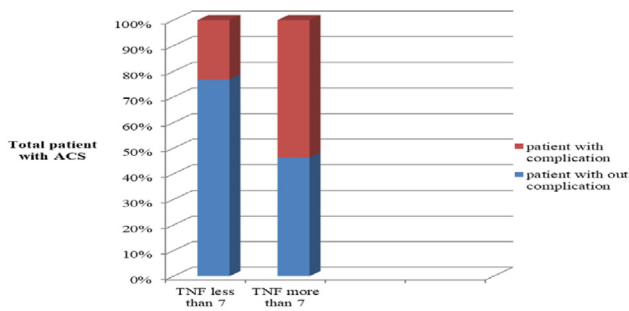


Fig. 4 Relation between the level of TNF-alpha & complications in patients with acute coronary syndrome.

Table 2. (Types & frequencies of complications in patients with MI & UA in the patient's groups)

Complications types	MI patients	Unstable angina patients	Total no	% from total no of patients
Recurrent anginal pain	7 (41.1%)	4 (23.5%)	11 (64.6%)	28.2%
Hemodynamic complication	3 (17.6%)	1 (5.8%)	4 (23.4%)	10.2%
Electrical complication	2 (11.7%)	0 (0%)	2 (11.7%)	5.1%
Total no	12 (70.5%)	5 (29.5%)	17 (100%)	43.5%

injury; TNF-alpha may have a certain role in the development of ischemia by causing release of endothelial adhesion molecules, activation of leukocytes and secretion of thrombocyte activating factors. TNF-alpha has been suspected to be related to the acute myocardial infarction pathogenesis.²² Koukkunen et al. was reported that a 3.5-fold increase was observed in fibrinogen and TNF-a in patients with ACS; They suggested two underlying sources of events; the first is the 'inflammation' factor that includes CRP, fibrinogen and IL-6, and the second is the 'injury' factor that includes troponin-T, creatine kinase-MB mass and TNF-a. Both of these factors were independent predictors of the risk of coronary death and other major coronary events. Both TNF-alpha and IL-6 were elevated in the coronary sinus compared with the aortic root in patients with ACS.²² Mizia-Stec et al; who was found significant increase in the level of TNF-a in patient with coronary artery disease.²³ Rajappa M, Sen SK, Sharma A. His study included population comprised of groups 1–3: 100 patients

each with acute myocardial infarction, unstable angina, and stable angina, respectively, and group 4 (100 healthy controls). Cytokine levels (interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor-alpha) were estimated by ELISA. Tumor necrosis factor-alpha levels were significantly higher in patients from groups 1 and 2, than in group 3 and controls. The ratios of pro-/anti-inflammatory cytokines in all the study groups increased significantly when patients with unstable angina were compared to other groups. In patients with acute myocardial infarction, tumor necrosis factor-alpha levels showed significant correlation with established risk factors such as body mass index, blood pressure, and lipid levels. Acute myocardial infarction patients show elevation in pro-inflammatory and anti-inflammatory cytokines, while unstable angina is associated with low levels of serum interleukin-10. These cytokines are markers of coronary artery disease and may be used for the identification of high-risk patients with unstable angina/acute myocardial infarction.²⁴ In our study we found there was significant increase in level of TNF-a in patients with acute coronary syndromes group as compared with control group (person without CAD) & also we do comparism between the level of TNF-a in MI patients & unstable angina patients & we found that the highest level of TNF-a were associated with acute MI more than UA suggesting that acute MI were associated with more inflammatory process than unstable angina & also we were compared the level of TNF-a & rate of occurrence of complications of acute coronary syndrome patients which show the highest levels of TNF-a were associated with more complications i.e. more inflammation more complications (Figure 4 and Table 2). Simon AD, Yazdani S who was studied the level of cytokines (IL-6, IL-1BETA, TNF-a) in patient with stable & unstable ACS; he was show significant difference in the level of IL-6& IL-1beta but not in TNF-a in the unstable coronary syndromes.²⁵

Conclusion

Increases in TNF-alpha levels were seen in patients with acute coronary syndrome. TNF-alpha levels are useful for identifying people at high risk for complications from unstable angina and acute myocardial infarction (MI) if they are elevated.

Conflict of Interest

None. ■

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