Brief Communication

Serum Levels of TNF-a, IL-6, and Selenium in Patients with Acute and Chronic Coronary Artery Disease

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ABSTRACT

Background: Selenium (Se) is part of the glutathione peroxidase enzyme complex (GSH-PX) that plays an important role in antioxidant mechanisms in body, also it has been demonstrated that populations with low Se intake have 2-3 times greater risk of ischemic heart disease. **Objective:** To determine the circulating levels of IL- 6, TNF-α, Cu, Zn, and Se in patients with chronic coronary artery disease (CCAD), acute myocardial infarction (AMI), and normal individuals. **Methods:** Patients were divided into two groups: 25 subjects with CCAD and 25 patients with AMI. The control group included 50 normal individuals who did not have any history of ischemic heart disease, and were sex and age matched with the patients. Blood samples were collected during the first hours after the onset of chest pain in AMI group. Serum concentration of Se, Cu, and Zn were determined by atomic absorption spectrometry and TNF-α and IL-6 levels were measured using ELISA method. **Results:** In both groups of patients there was a significant reduction in serum Se levels (82.36 + 11.31 μg/L in CCAD, 74.08+11.31μg/L in AMI, and 105+32.52μg/L in the control group, P=0.03). TNF-α titers were increased in AMI patients compared with CCAD and control group. Mean TNF-α levels were 37.44 pg/ml in CCAD, 914.32 pg/ml in AMI, and 4.80 pg/ml in the control group (P=0.01). Serum levels of IL-6 in CCAD and AMI patients were 3.28 ±15.55 pg/ml and 472±207.88 pg/ml, respectively, and 1.28 pg/ml in the control group (P=0.001). **Conclusion:** These findings confirm previous studies and demonstrate that patients suffering from AMI exhibit lower plasma concentrations of Se and higher concentrations of pro-inflammatory cytokines of TNF-α and IL-6.

Keywords: AMI, Selenium, Zinc, Copper, TNF-α, IL-6

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INTRODUCTION

It is known that individuals with low intake of Selenium (Se) have 2 to 3 fold increased risk of ischemic heart disease. Se binds to glutathione peroxidase (GSH-PX) enzyme, protecting red cell membrane and sub-cellular components against undesirable reactions induced by stress and free radicals.(1)
Se has a protective role in atherosclerosis by changing lipid profile; therefore, Se therapy in the active phase of myocardial infarction may decrease the chance of heart failure (2). The relationship between whole blood Se levels and risk of myocardial infarction has been investigated in a study conducted in New Zealand, revealing that a decrease in Se level in smokers should be regarded as a risk factor for heart disease.(3)
A correlation has been found between trace elements concentration (Cu, Zn, and Se) in heart tissue and physiologic parameters including cardiac output and ejection fraction of the heart.
TNF-α has a dose-dependent effect on ischemic myocardium, the lower dose may induce angiogenesis and the higher dose may induce development of connective tissue leading to scar formation. Increased plasma concentration of TNF-α has been found in patients with coronary artery disease (4). Stressed myocardium activates pro-inflammatory cytokines, such as TNF-α, producing abnormalities in myocyte contractile function. Moreover, soluble receptors that bind to TNF-α may be able to prevent and even reverse the damage. Pre-treatment with TNF-α antibody abolishes myocardial infarct size, resembling ischemic pre-conditioning (2).
In the present study we sought to determine the circulating levels of trace elements including Se, Cu, and Zn, pro-inflammatory cytokines of TNF-α and IL-6, and erythrocyte GSH-PX activity in patients with chronic coronary artery disease (CCAD), acute myocardial infarction (AMI), and a healthy control group.

PATIENTS AND METHODS

Fifty patients with coronary syndrome, including 25 patients with CCAD, diagnosed based on ECG, exercise tolerance test, and angiography findings, and 25 patients with AMI based on ECG and enzyme assays were enrolled into this study. 50 normal individuals, gender and age matched with patients and without any symptoms of ischemic heart disease were also selected. Blood samples were obtained during the first hours of chest pain onset in AMI group.
Samples were centrifuged and sera were stored at -25 ºC. Serum levels of Se, Cu, and Zn were determined by atomic absorption spectrometry, TNF-α and IL-6 values were measured using commercially available ELISA kit (Bender Med Systems-Austria) and erythrocyte GSH-PX activity was determined with Paglia and Valentine method.
The results were analyzed by SPSS package (version 9), T-test and variance analysis were used to compare groups.

RESULTS AND CONCLUSION

Se concentration was significantly reduced in CCAD and AMI patients compared with controls (82.36±11.31 µg/l in CCAD, 74.08±11.31 µg/l in AMI, and 105±32.52 µg/l in control group, P-value: 0.03). No significant difference was found between Zn and Cu serum concentrations in CCAD (0.98±0.22, 112±18), AMI (0.98±0.4, 115±20), and control group (0.96 ±0.24, 114±17) (P-value<0.05). (Table 1)

Table 1. Mean concentration of TNF- α, IL-6, erythrocyte GSH-PX, and trace elements in serum

Mean concentration of serum in groups	CCAD	AMI	Control	P value
Se pg/l	82.36±11.31	74.08±11.31	105.36 ± 32.52	0.03
Zn pg/l	0.98 ± 0.22	0.98 ± 0.21	0.96 ± 0.24	
Cu pg/l	112 ± 18	115 ± 20	114 ± 17	
TNF- α pg/ml	37.44	614.32	4.8	0.01
IL-6 ph/ml	3.28	472	1.28	0.001
Erythrocyte GSH-PX u/g	25.4	45	24	0.00

Mean TNF-α level was 37.44 pg/ml in CCAD, 614.32 pg/ml in AMI, and 4.80 pg/ml in control group (P-value=0.01). TNF-α was not detectable in 46% (n=47) of cases including 24% (n=6) of CCAD patients, and 82% (n=41) of controls. Serum level of IL-6 revealed significant difference between patient and control groups (3.28±15.55 pg/ml in CCAD, 472±207.88 pg/ml in AMI, and 1.28 pg/ml in control group, P-value= 0.001) (Table.1). IL-6 was not detectable in 70% (n=70) of cases including 84% (n=21) of CCAD patients, 8% (n=2) of AMI, and 94% (n= 47) of controls.

There was considerable difference in erythrocyte GSH-PX activity in AMI patients (45 u/g) compared with CCAD (25.40 u/g) and control group (24 u/g, P-value= 0.00).

Our results confirm the previous studies and demonstrate that patients suffering from AMI exhibit lower plasma concentration of Se. These data and those previously reported by others support the notion that selenium deficiency not only increases the risk of coronary artery diseases, but also increases the risk of acute events of myocardial infarction. (5, 6)

It has been reported that TNF-α and IL-6 values significantly increase during the first hours of AMI (7, 8). In addition, Ridker et al (9) found that elevated TNF-α serum levels are associated with smoking and obesity. TNF-α may be produced in early stages of AMI as a results of initiation of an inflammatory process resulting in tissue damage and myocardial necrosis.

Based on the results of current study, we conclude that measurement of TNF-α serum level in individuals with high risk of coronary artery disease would be an approach to determine whether increased levels of pro-inflammatory cytokines such as TNF-α is produced during the acute event or was present before the initiation of attack. If in fact TNF-α serum level raises weeks or months before the initiation myocardial infarction or during the episodes of chest pain , then one can consider the detection of this cytokine as a tool to predict the AMI in high risk subjects, considered as a risk factor for AMI.

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REFERENCES

1 Bor MV, Cevik C, Uslu I, Guneral F, Duzgun E. Selenium levels and glutathione peroxidase activities in patients with acute myocardial infarction. Acta Cardiol.1999;54:271-6.

2 Beaglehole R, Jackson R, Watkinson J, Scragg R, Yee RL. Decreased blood selenium and risk of myocardial infarction. Int J Epidemiol.1990;19 :918-22.

3 Cain BS, Harken AH, Meldrum DR. Therapeutic strategies to reduce TNF-alpha mediated cardiac contractile depression following ischemia and reperfusion. J Mol Cell Cardiol.1999 ;31:931-47.

4 Belosjorow S, Bolle I, Duschin A, Heusch G, Schulz R. TNF-alpha antibodies are as effective as ischemic preconditioning in reducing infarct size in rabbits. Am J Physiol.2003;284:H927-30.

5 Karla DK,Zhux,Ranchandani MK,et al;Increased myocardial gene expression of tumor necrosis factor-alpha and nitric oxide synthesis-2:A potential mechanism for depressed myocardial function in hibernating myocardium in humans.circulation.2002;105:1537.

6 Malave HA, Taylor AA, Nattama J, Deswal A, Mann DL. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure.Chest.2003;123:716-24.

7 Bennet AM, van Maarle MC, Hallqvist J, Morgenstern R, Frostegard J,Wiman B et al. Association of TNF-alpha serum levels and TNFA promoter polymorphisms with risk of myocardial infarction Atherosclerosis.2006;187:408-14.

8 Bennet AM, Alarcon-Riquelme M, Wiman B, de Faire U, Prokunina-Olsson L. Association of TNF-alpha serum levels and TNFA promoter polymorphisms with risk of myocardial infarction. Hum Immunol.2006;67:700-5.

9 Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of Tumor Necrosis Factor-a and Increased Risk of Recurrent Coronary Events After Myocardial Infarction.Circulation.2000;101:2149-53.