Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Comparison of serum levels of IL-6, IL-8, TGF-β and TNF-α in coronary artery diseases, stable angina and participants with normal coronary artery

Zahra Sepehri[1], Mohammad Masoumi[2*], Fatemeh Ruzbehi[3], Zohreh Kiani[4], Ali Akbar Nasiri[5], Farhad Kohan[6], Mahmood Sheikh Fathollahi[7], Mohammad Kazemi Arababadi[8], Derek Kennedy[9], Gholamreza Asadikaram[10]

[1] Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran
[2] Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[3] Physiology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[4] Department of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[5] Department of Internal Anesthesiology, Zabol University of Medical Sciences, Zabol, Iran
[6] Zabol University of Medical Sciences, Zabol, Iran
[7] Faculty of Medicine, and Immunology of Infectious Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[8] Faculty of Paramedicine and Immunology of Infectious Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[9] School of Natural Sciences, Eskitis Institute for Drug Discovery, Griffith University Nathan, Queensland, Australia
[10] Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

Correspondence to: masoomidr@yahoo.com

Received November 29, 2017; **Accepted** April 15, 2018; **Published** April 30, 2018

Doi: http://dx.doi.org/10.14715/cmb/2018.64.5.1

Abstract: Cytokines, which typically regulate the immune responses, play a role in cardiovascular diseases such as coronary artery diseases (CAD) and ischemic heart diseases (IHD). The aims of this study were to evaluate serum levels of IL-6, IL-8, TGF-β and TNF-α in patients with or without CAD, as well as stable angina, and to assess the effects of drug administration on the serum levels of these cytokines. Serum levels of the cytokines were analyzed in the three groups: patients with acute coronary syndrome, stable angina and participants with normal coronary arteries as controls. Cohort study of the patients showed that Nitrocontin was the only drug used in a significantly different pattern between the groups where it was used less frequently in patients with stable angina compared to the acute coronary syndrome or control groups. Serum levels of the evaluated cytokines were not different neither between the studied groups nor between the groups with variable Gensini scores. However, IL-8 in controls that were not engaged in regular exercise was higher than the controls performing regular exercise. In the stable angina group, TNF-α in non-smokers was higher than the smokers. It was revealed that serum levels of pro-inflammatory cytokines are not associated with atherosclerosis and stable angina in patients from the South-East of Iran. However, suppressed expression of TGF-β, may increase the risk of CAD. Exercise can reduce the risk of CAD through downregulation of pro-inflammatory cytokines.

Key words: Cytokine; Stable angina; Arthrosclerosis.

Introduction

Coronary artery diseases (CADs), especially atherosclerosis, are the most common causes of myocardial ischemia (1). Ischemic heart disease (IHD) may be clinically manifested as either stable angina or acute coronary syndrome (ACS). ACS can be divided into ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. There are two main types of angina: stable and unstable. Stable angina is the most common form of angina, with symptoms brought on by physical activity or stress. Unstable angina is defined as crescendo angina, angina at rest, and angina lasting more than 15 minutes (2).

The process of atherosclerosis has been associated with inflammation and cytokine imbalances (1). Although numerous factors can induce the disorder but complex changes driven by the immune system are considered as the major risk factors. It has been revealed that macrophages play a significant role in the induction of atherosclerosis (3) by the secretion of free radicals and cytokines (4,5). However, ethnic variation and genetic factors can also play important roles in the induction of atherosclerosis.

Cytokines, which are mostly produced by immune cells, have several important biological functions including inflammation, tissue damage as well as its regeneration (6). IL-6, IL-8 and tumor necrosis factor-alpha (TNF-α) are the main pro-inflammatory cytokines which are produced by several cells including macrophages and dendritic cells (7). These cytokines induce immune cell activation and recruitment and are also the main inducers of atherosclerosis (8). TNF-α, which is the main inducer of infectious shock and can induce hypotension, is the main cause of coma and death in the infected patients (9). Conversely, tumor growth factor-beta (TGF-β) is an anti-inflammatory cytokine which participates in tissue remodeling and angiogenesis (10). During atherosclerosis, vascular tissues are damaged by agents such as immune cells, therefore, it may be hypothesized that the pro-inflammatory cytokines like

IL-6, IL-8 and TNF-α, and anti-inflammatory cytokines like TGF-β may play key roles in the pathogenesis of the disease. Similar to the role of TNF-α in the infectious shock, cytokines may be involved in the induction of atherosclerosis and stable angina. Although inflammation plays a key role in the pathogenesis of atherosclerosis, but the results of clinical trials are still controversial, hence, the main aim of this study was to evaluate the serum levels of IL-6, IL-8, TGF-β and TNF-α in the patients with or without CAD as well as stable angina. Another aim of this study was to evaluate the correlation between serum cytokines and drugs used by the patients. Additionally, based on the fact that smoking, exercise and opium addiction are the critical factors which can alter susceptibilities to CAD, hence, another aim of this project was to evaluate the variables on the serum levels of IL-6, IL-8, TGF-β and TNF-α in the participants.

Materials and Methods

This is a cross-sectional study. All the subjects were candidates for coronary angiography. Participants were selected in the post-angiography ward of Shafa Hospital of Kerman, Iran. Data were collected using a questionnaire included demographic information such as, gender, age, education, family history of CAD, smoking and the use of specific drugs (11). All records were maintained as confidential data. Inclusion criteria of this study were: 1) Symptoms of ischemic heart disease and 2) Requirement for coronary angiography. Based on the previous studies, the exclusion criteria were: 1) Impossible to investigate the patient exactly, 2) History of congenital heart disease, heart surgery, nephropathic diseases, immune-mediated diseases, acute or chronic infectious diseases, diabetes, respiratory diseases, and physiological conditions related to the immune system functions such as pregnancy (12). All procedures of this study was approved by the Ethics Committee of the Zabol University of Medical Sciences, Zabol, Iran.

Coronary angiography was performed using Judkins method. All angiographic data were collected and reported by an experienced cardiologist. In total, 184 patients were divided into three groups with regards to their history, angiographic data, electrocardiogram (ECG) and cardiac enzyme assay including: 1) Acute coronary syndrome with one or more arterial stenosis (67 patients), 2) Stable angina (48 patients) and 3) Patients with normal coronary arteries as the control group (69 patients). In brief, standard angiography was performed for all of the patients and the severity of CAD was evaluated by comparing the diameter of the coronary artery stenosis and was considered significant with the lumen was ≥ 50 percent of any of the major epicardial coronary arteries. Gensini Scores were ranked as weak (scores 1-10), moderate (scores 10-50) and severe (more than 50). In patients who were opium users or smokers, data regarding age, exercise regimen and sex were obtained using a questionnaire. Regular exercise was defined for those who perform moderate physical activity for at least 150 minutes per week or vigorous activity for 75 minutes per week (13). Participants without stable angina and artery stenosis were matched regarding sex, age, opium consumption and smoking and they were considered as controls.

Preparation of blood samples

After at least a night's rest, fasting venous blood sample (5 mL) was collected from the participants. Samples were centrifuged at 2500 rpm for 7 min and the serum samples were collected in separate vials and kept at -20℃.

Cytokine assay

Serum levels of the cytokines (IL-6, IL-8, TGF-β and TNF-α) were evaluated using commercial kits (eBiosciences, USA) according to the manufacturer's guidelines.

Statistical analysis

Data were analyzed using SPSS version 18. One-Way ANOVA, t-test and Chi-square were used for analysis of the serum levels of cytokines among the groups regarding sex, opium consumption, smoking and exercise regimen.

Results

It was revealed that serum levels of IL-6 (P=0.502), IL-8 (P=0.996), TGF-β (P=0.095) and TNF-α (P=0.566) were not statistically different among the three groups (Figure 1, Panel A).

The results also demonstrated that serum levels of IL-6 (P=0.538), IL-8 (P=0.361), TGF-β (P=0.516) and (P=0.580) were not also altered among the groups with different Gensini scores (Figure 1, Panel B).

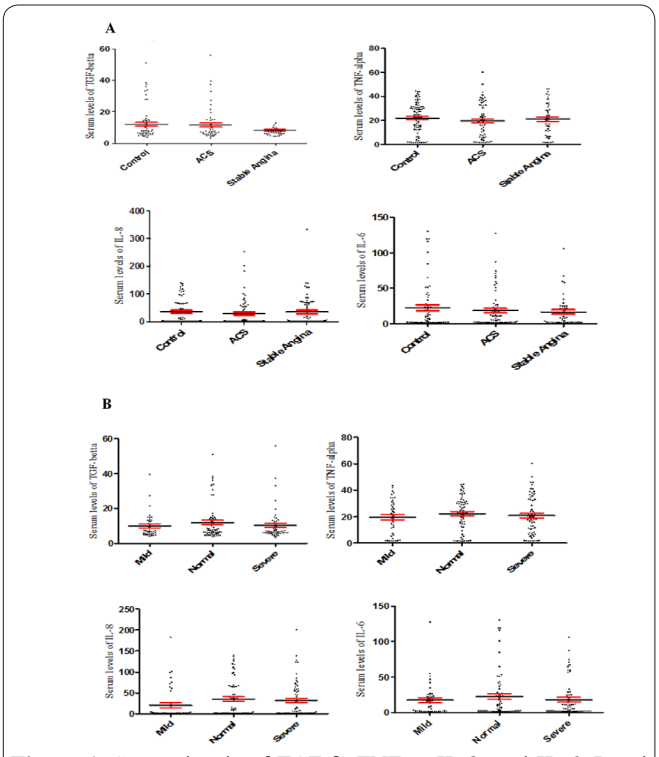

Figure 1. Serum levels of TGF-β, TNF-α, IL-8, and IL-6. Panel A evaluates patients with stable angina, acute coronary syndrome (ACS) and controls (A). The serum levels of TGF-β, TNF-α, IL-8 and IL-6 were not different between the groups. Panel B shows serum levels of TGF-β, TNF-α, IL-8, and IL-6 in the patients against their Gensini scores. The figure demonstrates that serum levels of the evaluated cytokines were not different between the groups.

Table 1. Serum levels of IL-6, IL-8, TGF-β and TNF-α in smoking versus non-smoking (A), opium-addicted versus non-addicted (B) and male versus female (C) participants.

A

Group	Cytokine	Smoking Participants	Non-smoking Participants	P-value
Control	IL-6	15.34 ± 5.77	24.01 ± 4.61	0.443
	IL-8	46.35 ± 14.17	33.50 ± 5.87	0.399
	TGF-β	9.19 ± 3.11	12.42 ± 1.44	0.393
	TNF-α	20.41 ± 3.38	22.60 ± 1.75	0.620
Acute coronary syndrome	IL-6	14.24 ± 3.33	20.77 ± 4.19	0.228
	IL-8	36.15 ± 10.87	35.20 ± 11.80	0.961
	TGF-β	9.70 ±1.63	12.60 ± 1.76	0.310
	TNF-α	20.91 ± 2.95	19.24 ± 2.20	0.664
Stable angina	IL-6	16.31 ± 3.51	16.78 ± 3.74	0.958
	IL-8	33.88 ± 16.64	36.85 ± 10.19	0.900
	TGF-β	11.51 ± 2.83	7.37 ± 0.50	0.191
	TNF-α*	11.16 ± 2.65	23.20 ± 2.13	0.018

B

Group	Cytokine	Opium-addicted Participant	Non-opium addicted Participant	P-value
Control	IL-6	19.31 ± 7.04	23.69 ± 4.79	0.651
	IL-8	30.45 ± 9.13	36.92 ± 6.49	0.620
	TGF-β	11.07 ± 2.56	12.21 ± 1.53	0.720
	TNF-α	18.72 ± 3.27	23.41 ± 1.77	0.203
Acute coronary syndrome	IL-6	13.56 ± 3.50	22.38 ± 4.60	0.132
	IL-8	44.68 ± 13.74	29.52 ± 11.51	0.405
	TGF-β	10.19 ± 1.65	12.85 ± 1.95	0.322
	TNF-α	22.19 ± 2.84	18.10 ± 2.23	0.258
Stable angina	IL-6	16.55 ± 6.67	16.80 ± 3.42	0.971
	IL-8	30.00 ± 9.39	40.41 ± 13.28	0.571
	TGF-β	8.61 ± 1.45	7.89 ± 0.66	0.628
	TNF-α	19.37 ± 3.20	22.25 ± 2.44	0.476

C

Group	Cytokine	Male	Female	P-value
Control	IL-6	21.06 ± 5.86	24.14 ± 5.57	0.705
	IL-8	32.78 ± 8.29	37.95 ± 7.12	0.637
	TGF-β	12.40 ± 1.96	11.54 ± 1.76	0.745
	TNF-α	21.91 ± 2.23	22.59 ± 2.22	0.832
Acute coronary syndrome	IL-6	18.87 ± 3.16	18.67 ± 8.49	0.978
	IL-8	34.64 ± 10.46	38.14 ± 16.39	0.866
	TGF-β	11.43 ± 1.54	12.48 ± 1.54	0.735
	TNF-α	20.95 ± 1.99	16.20 ± 3.68	0.246
Stable angina	IL-6	13.41 ±3.35	21.23 ± 5.98	0.231
	IL-8	44.36 ± 14.09	24.93 ± 7.23	0.228
	TGF-β	8.05 ± 1.05	8.41 ± 0.89	0.811
	TNF-α	21.10 ± 2.75	21.21 ± 2.63	0.978

Data are expressed as mean ± SE (standard error of mean).

*Tables 1-3 show that serum levels of TNF-α in the stable angina group and non-smoking participants were significantly higher than the smoking participants.

Evaluation of cytokine serum levels in smokers and non-smokers in each group demonstrated that TNF-α in non-smokers was significantly (P=0.018) higher than the smokers with stable angina (Table 1). The serum levels of other cytokines in non-smokers compared with smokers in other groups were not statistically significant (Table 1). Furthermore, a statistical analysis revealed that the smoking and non-smoking patients with stable angina received similar patterns of drugs (Aspirin (P=1.0), Clopidogrel (P=1.0), Atorvastatin (P=0.437), Metoprolol (P=0.418), Nitrocontin (P=1.0) and Losartan (P=1.0)), therefore, the use of these drugs cannot be considered as a causative agent.

Serum levels of IL-8 in participants with regular exercise in control group were significantly lower than those with non-regular exercise in the control group (P=0.035). Serum levels of IL-8 between participants with regular exercise and non-regular exercise in other groups were not significantly different (Table 2). The serum levels of IL-6, TGF-β and TNF-α between participants with regular exercise and non-regular exercise in all groups were not significantly different (Table 2).

Table 2. Serum levels of IL-6, IL-8, TGF-β and TNF-α in participants with regular versus non-regular exercise.

Group	Cytokine	Participant with Regular Exercise	Participant with Non- Regular Exercise	P-value
Control	IL-6	14.55 ± 7.56	23.36 ± 4.29	0.565
	IL-8*	10.92 ± 8.78	37.46 ± 5.74	0.035
	TGF-β	6.25 ± 0.81	12.35 ± 1.38	0.260
	TNF-α	21.86 ± 5.46	22.30 ± 1.64	0.940
Acute coronary syndrome	IL-6	17.62 ± 6.63	19.03 ± 3.49	0.873
	IL-8	45.37 ± 17.31	33.72 ± 9.95	0.639
	TGF-β	11.00 ± 2.98	11.81 ± 1.47	0.825
	TNF-α	21.91 ± 5.54	19.37 ± 1.84	0.604
Stable angina	IL-6	7.70 ± 2.92	18.37 ± 3.69	0.230
	IL-8	10.64 ± 8.12	40.95 ± 10.17	0.222
	TGF-β	5.58 ± 0.41	8.66 ± 0.82	0.129
	TNF-α	19.00 ± 5.84	21.52 ±2.06	0.648

Data are expressed as mean ± SE (standard error of mean).

Statistical analysis also showed that the participants with regular exercise in the control group received similar patterns of drugs when compared with controls with no regular exercise, therefore, drug regimen cannot be considered as a causative agent for the differences in IL-8 levels. The table shows that serum levels of IL-8 in the control group, were significantly increased in patients with non-regular exercise compared to those with regular exercise.

The results also demonstrated that serum levels of IL-6, IL-8, TGF-β and TNF-α in the opium- addicted patients, compared to non-addicted patients in any subgroup were not significantly different (Table 1, panel B).

The results demonstrated that the three evaluated groups were similar in the use of prescribed or over-the-counter drugs with the exception of Nitrocontin, which had been administrated more in controls and ASC groups compared with those with stable angina (Table 3).

Discussion

Cytokines play key roles in cells proliferation and also the fibrogenic disorders like atherosclerosis (8). Furthermore, there are significant overlap and interplay between the nervous and cardiovascular systems with the immune system via the cytokines network (14). Therefore, it may be hypothesized that IHD has a correlation with cytokine networks. The results of this study showed that serum levels of IL-6, IL-8, TGF-β and TNF-α were not changed among patients with ACS and stable angina in comparison to the controls. Therefore, it seems that the cytokines have no biologically significant function in determining the pathology of ACS and stable angina in the patients. Additionally, as mentioned in Table 3, Nitrocontin was prescribed less frequently to the stable angina group compared to the control and ASC groups. Therefore, it seems that Nitrocontin has no effect on the serum levels of the evaluated cytokines. Similar to this study, a study by Song et al (2004) also showed that IL-6 does not play a significant role in atherogenesis (15). It should be noted that in this study, only a total of 184 patients (67 in the acute coronary syndrome group, 48 in the stable angina group and 69 in the control group) were evaluated. This is the limitation of the present study and further studies with a larger sample size are required to improve the power of the study and to reveal statistically significant data between the groups.

Table 3. Frequency of prescribed and over-the-counter drug usage in the three groups.

Drugs	ASC	Stable Angina	P-value
Aspirin	63 (94.0)	47 (97.9)	0.691*
Clopidogrel	11 (16.4)	2 (4.2)	0.065
Atorvastatin	21 (31.3)	21 (43.8)	0.375
Metoprolol	11 (16.4)	13 (27.1)	0.377
Nitrocontin	61 (91.0)	21 (43.8)	<0.001
Losartan	9 (13.4)	9 (18.8)	0.720

Data are expressed as n (%). *Frequency of data was analyzed using Fisher's exact test for Aspirin and chi-square test for other drugs among the three groups. P<0.05 was statistically considered as significant differences.

Although, this study showed no correlation between the cytokines and ACS and stable angina, but several previous studies demonstrated a relationship between the cytokines and CAD. For instance, Saremi et al., (2009) reported that IL-6 was significantly associated with changes in the coronary artery calcium score in type 2 diabetic patients (16). Another study revealed that serum levels of IL-6 were positively correlated with carotid intima-media thickness (17). Haddy et al., (2003) demonstrated that serum levels of IL-6, but not TNF-α, are closely associated with atherosclerosis risk factors (18). Marino and colleagues (2015) showed that in patients with carotid plaques, circulating and intraplaque polymorphonuclear (PMN)cells produce IL-8 which is essential for plaque development and progression (19). Investigations demonstrated that statins and renin-angiotensin blockers regulate the production of pro-inflammatory cytokines (20,21). For example, Briasoulis et al., (2016) reported that the drugs have a negative effect on the cytokines production (22). Results from Hassanin and colleagues (2014) supported these findings and showed the regulatory effects of renin-angiotensin blockers on the production of TNF-α (23). The patients who participated in the present study received similar patterns of statins and renin-angiotensin blockers, hence, it seems that the drug can decrease serum

levels of pro-inflammatory cytokines, which may have been normally elevated in the CAD through disease progression.

McCaffrey (2008) reported that the cells of atherosclerotic lesions of human arteries produce adequate levels of TGF-β, as a major orchestrator of the vascular repair process, but are resistant to some cytokine functions including anti-proliferative and apoptotic effects (24). However, this study cannot confirm the results because the serum levels of TGF-β were not altered between CAD, stable angina and controls. Based on the fact that TGF-β is a main factor for repairing the vessels, especially after atherosclerosis (25), therefore, more investigations are required to determine the main roles of TGF-β in CAD and stable angina. Therefore, it is possible that a mechanism which leads to the induction of ACS in our patients is related to disrupted production of TGF-β.

In this study, no correlation between IL-6, IL-8, TGF-β and TNF-α in ACS and stable angina was reported. However, it should be noted that cytokines act in a network manner and there can be redundancies within these systems, hence, other cytokines, which normally act in a redundant manner, may take the role of inducing inflammation and CAD. For example, Hulthe et al., (2003) reported that IL-18 is associated with atherosclerosis independently of IL-6 (26).

The results also revealed that serum levels of the pro-inflammatory cytokine IL-8, were suppressed in the controls, but not in the ACS and stable angina groups, with regular exercise in comparison to those with non-regular exercise. The patterns of drug regimens were similar in the patients with regular exercise in comparison to those with non-regular exercise in the control group, so the drugs have no effect on the cytokine serum levels in these groups. Therefore, it seems that the variations of IL-8 between the participants were not associated with the types of drugs given to the patients. Therefore, it may be concluded that regular exercise in people with normal coronary artery can inhibit chronic inflammation via downregulation of pro-inflammatory cytokines like IL-8. Based on the fact that IL-8 is the main factor for recruitment of neutrophils, hence, it may be hypothesized that regular exercise is associated with decreased chronic inflammation in the non-CAD individuals in IL-8-dependent manner. Additionally, the results showed that the serum levels of TNF-α in non-smokers were higher than the smokers with stable angina. Considering that the groups were given similar prescribed or over-the-counter drugs, it can be concluded that smoking leads to the development of stable angina through the other mechanisms rather than the production of pro-inflammatory cytokines.

According to the results of the present study, it seems that the evaluated cytokines have no significant participation in determining the pathology of ACS and stable angina in the patients. It could be concluded that regular exercise can inhibit progression of the disease through downregulation of pro-inflammatory cytokines.

Acknowledgements
Authors would like to thank all people who participated in this study.

Statement of Ethics
The patients who participated in this project have filled out the informed written consent form and all procedures of the study was approved by the Ethics Committee of the Zabol University of Medical Sciences, Zabol, Iran.

Financial disclosures
This study was funded by the Zabol University of Medical Sciences.

Conflict of interest
Authors have no conflict of interest to declare.

References

1. El-Menyar AA. Cytokines and coronary artery disease: the state of the art. Critical pathways in cardiology. 2008,7(2):139-51.
2. Tobin KJ. Stable angina pectoris: what does the current clinical evidence tell us. J Am Osteopath Assoc. 2010,110(7):364-70.
3. Suzuki H, Kurihara Y, Takeya M, Kamada N, Kataoka M, Jishage K, Ueda O, Sakaguchi H, Higashi T, Suzuki T. A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. 1997.
4. Madrigal-Matute J, Fernandez-Garcia C-E, Blanco-Colio LM, Burillo E, Fortuño A, Martinez-Pinna R, Llamas-Granda P, Beloqui O, Egido J, Zalba G. Thioredoxin-1/peroxiredoxin-1 as sensors of oxidative stress mediated by NADPH oxidase activity in atherosclerosis. Free Radical Biology and Medicine. 2015,86:352-61.
5. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. Science. 2015,349(6245):316-20.
6. Arababadi MK, Aminzadeh F, Hassanshahi G, Khoramdelazad H, Karimabad MN, zarandi ER, Rezayati M, Kennedy D. Cytokines in Preterm Delivery. LabMedicine. 2012,43(4):131-4.
7. Fadok V, McDonald P, Bratton D, Henson P. Regulation of macrophage cytokine production by phagocytosis of apoptotic and post-apoptotic cells. Biochemical Society Transactions. 1998,26(4):653-6.
8. Correa CR, Dias-Melicio LA, Calvi SA, Lastoria S, Soares AM. Activation of monocytes and cytokine production in patients with peripheral atherosclerosis obliterans. J Inflamm (Lond). 2011,8:23.
9. Shi-lin D, Yuan X, Zhan S, Luo-jia T, Chao-yang T. Trametinib, a novel MEK kinase inhibitor, suppresses lipopolysaccharide-induced tumor necrosis factor (TNF)-α production and endotoxin shock. Biochemical and biophysical research communications. 2015,458(3):667-73.
10. Karimi-Googheri M, Daneshvar H, Nosratabadi R, Zare-Bidaki M, Hassanshahi G, Ebrahim M, Arababadi MK, Kennedy D. Important roles played by TGF-beta in hepatitis B infection. J Med Virol. 2013.
11. Djoussé L, Gaziano JM. Alcohol consumption and risk of heart failure in the Physicians' Health Study I. Circulation. 2007,115(1):34-9.
12. Rajman I, Kendall M, Cramb R, Holder R, Salih M, Gammage M. Investigation of low density lipoprotein subfractions as a coronary risk factor in normotriglyceridaemic men. Atherosclerosis. 1996,125(2):231-42.
13. Health UDo, Services H, Health UDo, Services H. Physical activity guidelines for Americans. 2008.p. (http://www.health.gov/paguidelines/pdf/paguide).
14. Agarwal I, Glazer NL, Barasch E, Biggs ML, Djousse L, Fitzpatrick AL, Gottdiener JS, Ix JH, Kizer JR, Rimm EB. Fibrosis-Related Biomarkers and Incident Cardiovascular Disease in Older Adults: The Cardiovascular Health Study. Circulation: Arrhythmia and Electrophysiology. 2014:CIRCEP. 114.001610.
15. Song L, Schindler C. IL-6 and the acute phase response in murine atherosclerosis. Atherosclerosis. 2004,177(1):43-51.
16. Saremi A, Anderson RJ, Luo P, Moritz TE, Schwenke DC,

Allison M, Reaven PD. Association between IL-6 and the extent of coronary atherosclerosis in the veterans affairs diabetes trial (VADT). Atherosclerosis. 2009,203(2):610-4.
17. Nishida M, Moriyama T, Ishii K, Takashima S, Yoshizaki K, Sugita Y, Yamauchi-Takihara K. Effects of IL-6, adiponectin, CRP and metabolic syndrome on subclinical atherosclerosis. Clinica Chimica Acta. 2007,384(1):99-104.
18. Haddy N, Sass C, Droesch S, Zaiou M, Siest G, Ponthieux A, Lambert D, Visvikis S. IL-6, TNF-α and atherosclerosis risk indicators in a healthy family population: the STANISLAS cohort. Atherosclerosis. 2003,170(2):277-83.
19. Marino F, Tozzi M, Schembri L, Ferraro S, Tarallo A, Scanzano A, Legnaro M, Castelli P, Cosentino M. Production of IL-8, VEGF and Elastase by Circulating and Intraplaque Neutrophils in Patients with Carotid Atherosclerosis. 2015.
20. Oikonomou E, Siasos G, Zaromitidou M, Hatzis G, Mourouzis K, Chrysohoou C, Zisimos K, Mazaris S, Tourikis P, Athanasiou D, Stefanadis C, Papavassiliou AG, Tousoulis D. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients. Atherosclerosis. 2015,238(2):159-64.
21. Moreira DM, da Silva RL, Vieira JL, Fattah T, Lueneberg ME, Gottschall CA. Role of vascular inflammation in coronary artery disease: potential of anti-inflammatory drugs in the prevention of atherothrombosis. Inflammation and anti-inflammatory drugs in coronary artery disease. Am J Cardiovasc Drugs. 2015,15(1):1-11.
22. Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. Heart Fail Rev. 2016,21(2):169-76.
23. Hassanin A, Malek HA. Effect of renin inhibition on adipokines in diabetic rats. Pak J Pharm Sci. 2014,27(4):767-72.
24. McCaffrey T. TGF-beta signaling in atherosclerosis and restenosis. Frontiers in bioscience (Scholar edition). 2008,1:236-45.
25. Robertson A-KL, Rudling M, Zhou X, Gorelik L, Flavell RA, Hansson GK. Disruption of TGF-β signaling in T cells accelerates atherosclerosis. Journal of Clinical Investigation. 2003,112(9):1342.
26. Hulthe J, McPheat W, Samnegård A, Tornvall P, Hamsten A, Eriksson P. Plasma interleukin (IL)-18 concentrations is elevated in patients with previous myocardial infarction and related to severity of coronary atherosclerosis independently of C-reactive protein and IL-6. Atherosclerosis. 2006,188(2):450-4.