

## A Study on Oxidative Stress in Patients with Angina Pectoris Admitted to Coronary Care Unit

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Article information	Abstract
<p>Article history: Received: 20 July 2011 Accepted: 14 Sep 2011 Available online: 30 Oct 2012 ZJRMS 2013; 15(3): 20-25</p> <p>Keywords: Oxidative stress Lipid profile Oxidant and antioxidants Angina pectoris</p> <p>*Corresponding author at: Department of Nutrition, Zahedan Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: mkarajibani@gmail.com</p>	<p><b>Background:</b> The oxidative stress causes biological damages in addition to the increase of cardiovascular system diseases such as angina pectoris. The present study aims to determine the oxidant and anti-oxidant (enzymatic and non-enzymatic) status in patients with angina pectoris.</p> <p><b>Materials and Methods:</b> In this descriptive-analytical study, 24 hospitalized patients with angina pectoris and 63 healthy people, as control group, were selected. Blood fats including cholesterol, triglyceride and HDL were determined through the enzymatic method and the LDL was determined using Friedewald formula. The heparinized blood was used to measure superoxide dismutase, glutathione peroxidase (GPx), and plasma to determine malondialdehyde (MDA) and vitamin C through spectrophotometric method and total antioxidant capacity (TAC) through ferric reducing ability of plasma (FRAP). Vitamins A and E of serum were determined through the chromatography method in two groups and SPSS-11.5 software was used for statistical analysis. The degree of error in the tests was calculated as <math>p &lt; 0.05</math>.</p> <p><b>Results:</b> A significant difference was observed in blood fat contents as well as the oxidant and anti-oxidant (enzymatic and non-enzymatic) indices between the two groups (<math>p &lt; 0.001</math>). A positive and significant relationship was observed between superoxide dismutase and vitamin C, MDA and LDL. However, this relationship with HDL and TAC was negative and significant (<math>p &lt; 0.05</math>).</p> <p><b>Conclusion:</b> With respect to the significant decrease of anti-oxidants and TAC and the increase of lipid peroxidation as well as the relationship between the different indices, the oxidative stress caused anti-oxidants system suppression in patients.</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

### Introduction

Angina pectoris often occurs when heart needs a lot of blood. These patients usually complain about a pain in chest like heaviness, pressure and uneasiness [1, 2]. In the stable angina, there is no balance between oxygenation of cardiac muscles tissue and the need of tissue to oxygen [1]. The clinical symptom is more severe instable angina and it usually occurs at rest. Its most frequent symptom is the decrease of weight of heart muscle tissue in coronary arteries, which is narrowed or become blocked due to fat deposition and vessels arteriosclerosis [3].

In separate studies, Young, Woodside and Furukowa reported that oxidative stress plays an important role in pathogenesis of the progressive and chronic diseases such as arteriosclerosis, diabetes as well as cancer. On the other hand, producing different kinds of oxygen leads to biological damage of organism and potentially aggravates symptoms [3, 4]. Studies indicate that there is a close relationship between the production of kind of active oxygen (ROS) and analysis of the anti-oxidant system [3]. The oxidative stress causes damage to DNA, fats and proteins in such a way that abnormalities occur in the

cellular and molecular hemostasis [5]. Free radicals are created in body by different mechanisms, including two androgenesis systems (necessary metabolic processes such as oxidative phosphorylation and cellular respiration in mitochondria) and environmental factors such as, light, heat and metals [6].

Aviram reported that oxidation of lipids plays an important role in developing cardiovascular diseases and oxidation of low-density lipoprotein (LDL) which is an important factor in preliminary atherosclerosis [7]. Madamanchi et al. observed that atherosclerosis is the most frequent complication of cardiovascular diseases [8] which occurs by LDL oxidation in the cells in walls of arteries. LDL oxidation forms a fatty steak which causes damages to endothelium [9]. Also, free radicals and different kinds of active oxygen are not always harmful. Rather, they are necessary for lots of cellular functions, which are biologically useful, such as activation of phagocytosis system to destroy some bacteria and fungi [10]. On the other hand, aerobic organism protects body by the anti-oxidant system, which includes angiogenesis and exogenesis compounds [11, 12].

Angiogenesis anti-oxidants are important as far as cellular maintenance and health although care should be taken to intake anti-oxidants from diets [12]. Anti-oxidants have a dynamic status in body, which is influenced by different factors. Anti-oxidant system in body has two enzymatic forms, including (catalase, glutathione peroxidase and superoxide dismutase) and non-enzymatic, including water- and fat soluble vitamins with various physical and chemical properties [3]. In addition to the above systems, there are compounds such as flavonoids, phytochemicals, albumin and urate [13]. Catalase turns hydrogen peroxide into water and oxygen molecule within two stages. The most activity of catalase occurs in liver and red cells, although it is active in other tissues as well [5].

Superoxide dismutase (SOD) causes dismutation of superoxide into oxygen molecule and hydrogen peroxide [3, 6]. Accordingly, hydrogen peroxide turns into water by glutathione peroxidase. The high ratio of reduced form of glutathione to its oxidized form is due to the activity of glutathione reductase enzyme [3]. The oxidized form of glutathione was reported to be in coronary sinus of human body. The oxidized form of glutathione (GSSG) has a positive relation with ischemia. Under this condition, tissues need its reduced form (GSH) [14].

Vitamin E is the most important non-enzymatic anti-oxidants, which is soluble in fat. Principally, vitamin E exists in VLDL and LDL and prevents oxidation of unsaturated fatty acids by free radicals [3]. In addition, vitamin E is a potential anti-oxidant, its effectiveness increases by other anti-oxidants such as vitamin C, selenium and beta-carotene, and increases the protective effect of HDL [9, 14]. Vitamin C has a maintaining effect on vitamin E so that it is reduced by vitamin C after neutralizing the radicals by vitamin E. Therefore, it increases the potential of vitamin E in a biologic environment. Vitamin C is the leading defense system against oxidative stress [3].

Due to the importance of the antioxidative enzymes in neutralizing the effects of oxidants, special attentions have been paid to them. In particular, the number of cardiovascular diseases, including angina pectoris, is increasing in Zahedan. Considering the importance of this issue, the present research aims to study the oxidative stress based on the oxidant and anti-oxidant (enzymatic and non-enzymatic) indices and the relationships among them in patients with angina pectoris hospitalized in Zahedan Khatam al-Anbia Hospital.

## Materials and Methods

This study is conducted on 24 patients (13 men and 11 women) with the average age of  $57.4 \pm 13.9$  years and symptoms of angina pectoris who were hospitalized in the CCU of Zahedan Khatam al-Anbia Hospital in 2006. The criteria to enter the patients into the study has been diagnosis by cardiologists including unstable angina, a pain in chest lasting for 3 hours, echocardiography changes and the increase of activity of CK and CK-MB

enzymes. In addition, the control group comprised 63 healthy people (41 men and 22 women) with the average age of  $56.4 \pm 11.3$  years.

The control group had normal electrocardiogram, with no record of heart disease, hypertension, diabetes, liver and kidney diseases, malignancy, pregnancy, surgery and/or severe medical problem during the last 3 months. None of the groups had received anti-oxidant vitamin supplements. Meanwhile, the control group had the demographic, social, economic and dietary conditions similar to those of the subject group, but without problems. This study was confirmed by the ethics committee of Zahedan University of Medical Sciences and written informed consents were received from the people under study.

Seven milliliters of the blood of people under study was taken in different test tubes. The heparinized blood was used to measure the superoxide dismutase enzymes, glutathione peroxidase, vitamin C and malondialdehyde (MDA) and serum sample to measure vitamins A and E. The MDA was determined through the spectrophotometric method (thiobarbituric acid, TBARS) and the absorption degree of samples was determined in 530 nm. The MDA concentration was expressed by Mmol per liter of plasma [15]. The activity of superoxide dismutase (SOD) determined according to the production of anion-  $O_2^-$  by grantyn / xanthine oxidase using a Ransod kit (made in the UK). The activity of glutathione peroxidase (GPx) was determined using Randox kit (made in the UK) using the Paglia & Valentin method in 340 nm. The activity of GPx enzyme, the same as SOD enzyme activity, was expressed as per units per gram of hemoglobin (U/g Hb) [16, 17].

Vitamins A and E were determined after extraction by hexane through the chromatography method (HPLC), WATERS, NOBA-PACK C184 Micrometer,  $3.9 \times 150$  mml in 325 nm and 292 nm, respectively [18]. The quantity of vitamin C of plasma was measured using 2 and 4 dinitrophenylhydrazine reagent through the spectrophotometric method in the wavelength of 520 nm [18].

The total antioxidant capacity (TAC) was calculated using ferric reducing ability of plasma (FRAP) in low pH using the spectrophotometric in 593nm [19]. Moreover, the quantity of serum fats, including cholesterol, triglyceride and HDL was specified through the enzymatic method using Pars Azmoon commercial kit, made in Iran [20]. The quantity of LDL was calculated by Friedewald formula [18]. The SPSS-11.5 software was used for statistical analysis. Pearson correlation coefficient was used to compare the two groups of *t*-test and to communicate between the different variables.  $p < 0.05$  was regarded as the significance level of the differences between the groups.

## Results

Table 1 represents the general specifications of the patients with angina pectoris and the control group. The results of research indicated that there is a significant

difference in the indices of CPK, CK-MB, hypertension and blood lipids, including cholesterol, triglyceride, LDL-c and HDL-c between the two groups ( $p < 0.05$ ). However, the difference between age and body mass index was not significant (Table 1).

The findings also indicated that there is a significant difference between the two groups on oxidant index of MDA and TAC and other enzymatic indices, including GPx and superoxide dismutase and also a non-enzymatic,

including vitamins A, E and C between the two groups ( $p < 0.001$ ) (Table 2). A positive and significant relationship was observed between the MDA and LDL indices ( $p=0.04$ ). However, this relationship with HDL ( $p=0.03$ ) and TAC ( $p=0.001$ ) was negative and significant. A positive and significant relationship was observed between the TAC index and vitamin C ( $p=0.04$ ) and superoxide dismutase ( $p=0.03$ ) as well as between superoxide dismutase and vitamin C ( $p=0.001$ ) (Fig. 1).

**Table 1.** General characteristics, biochemical and enzymatic parameters of study groups

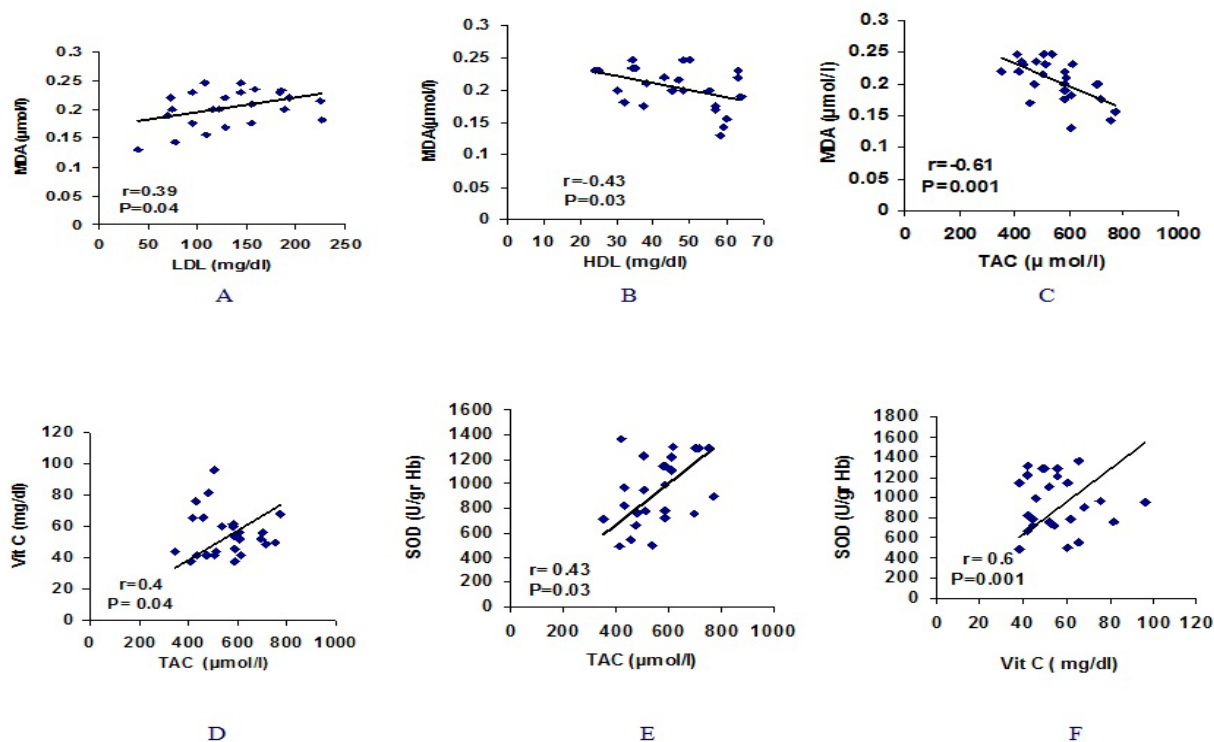
Parameters	Patients (n=24)	Control (n=63)	p-Value
Sex ( M/F)	13/11	41/22	-
Age (year)	57.4±11.0	56.4±11.3	*NS
BMI (kg/m <sup>2</sup> )	26.4±4.7	26.5±4.6	*NS
Systolic BP(mm/Hg)	146.0±19.4	113.1±12.6	$p < 0.0001$
Diastolic BP(mm/Hg)	95.0±13.4	72.6±9.4	$p < 0.0001$
CPK (U/L)	291±329	101.6±38.8	$p < 0.001$
CKMB (U/L)	56.5±47.1	14.8±4.8	$p < 0.001$
Cholesterol (mg/dL)	214.0±43.0	180.2±29.3	$p < 0.001$
Triglyceride (mg/dL)	139.7±76.0	114.3±45.1	$p < 0.001$
LDL-C (mg/dL)	140.4±50.1	99.4±27.2	$p < 0.001$
HDL-C (mg/dL)	45.2±12.0	57.0±12.6	$p < 0.001$

Values are expressed as Mean±SD

\* Not significant

**Table 2.** Oxidant and antioxidants status of study groups

Parameters	Patients(n=24)	Control (n=63)	p-Value
MDA (μmol/L)	0.03±0.21	0.12±0.02	$p < 0.0001$
TAC (μmol/L)	540.0±106.5	785.5±158.5	$p < 0.0001$
SOD (U/gHb)	919.0±276.4	2273.5±552.2	$p < 0.0001$
GPx (U/grHb)	13.5±3.0	30.7±7.7	$p < 0.0001$
Vitamin A (μg/dL)	53.7±16.1	60.4±12.8	$p < 0.02$
Vitamin E (μg/dL)	104.0±540.4	696.2±169.5	$p < 0.001$
Vitamin C (mg/dL)	0.21±0.55	1.2±0.4	$p < 0.001$



**Figure 1.** Correlation between different parameters of oxidant, antioxidants and lipid profiles of study groups

## Discussion

In this study, a considerable difference was observed on oxidant and anti-oxidant indices between angina pectoris patients and healthy people. The significant increase in MDA quantity, as a product of lipid peroxidation and the decrease of TAC, indicated the existence of oxidative stress in the patients under study. The results specified that with the decrease of the activity of superoxide dismutase and GPx, the oxidation of fats increased. In addition, the quantities of non-enzymatic anti-oxidant such as vitamins A, E and C decreased as well.

There were no differences between the body mass index of both the healthy and patient groups. Keaney et al. reported that with the increase of body mass index, the oxidative stress increases and anti-oxidant reserves are depleted [21]. Although the mean of the blood pressure in the patients under study was almost acceptable, with respect to its extent, it probably exposes most of them to the risk of oxidative stress. The increase of oxygen free radicals such as OH<sup>-</sup>, H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub><sup>-</sup> may be as effective as the other conditions such as myocardial infarction and atherosclerosis in contractions of smooth muscle cells which cause resistance against blood flow and damage to organs [22].

Nyysonen et al. suggested that lack of vitamin C causes hypertension in myocardial infarction patients [23]. In addition, oxidative stress in people with hypertension increases free oxygen contents and lack of nitrogen oxide (NO) which probably causes the increase of environmental arteriole contraction. The oxidative stress may damage the endothelial cell function and increase vascular activity to different stimulus such as oxygen [22]. The clinical and epidemiological studies indicate that the increase of LDL contents leads to development of atherosclerosis [24]. However, HDL, due to the inhibition of LDL oxidation, plays an important role in prevention or decrease of atherosclerosis [25]. Serdar et al. and Pasupathi et al., in two separate studies, have reported the significant increase of cholesterol, triglyceride and LDL contents and the significant decrease of HDL contents in coronary artery and myocardial infarction patients, respectively as compared with healthy people [16, 26].

The results of the research indicated that there is a significant difference on indices of blood lipid between the two groups. In general, development of lipid oxidation depends upon some factors, including free radicals, the existence of lipid compounds and anti-oxidant system activity [27].

In the present study, the significant increase of MDA is probably due to the excessive production of active oxygen, which is because of LDL change and/or weak anti-oxidant condition. This is confirmed in the positive relationship between MDA and LDL and the negative relationship with HDL in the patients under study. Although the average contents of cholesterol and triglyceride were natural in the above study, the relationship between different contents of blood fats with oxidant and anti-oxidant indices indicates the clinical condition of angina pectoris in connection with oxidative

stress phenomenon. Serdar and Macmurray, in separate studies on coronary patients and/or those with chronic heart failure observed the increase of MDA [16, 28].

Studies specified that the activity of GPx and SOD enzymes had a significant decrease, as compared with the control group. A more increase in GPx was observed concurrent with lipid oxidation. Similarly, the decrease of GPx and SOD enzymes contents in cardiovascular patients was reported in different studies [16]. The decrease of GPx activity may be in connection with the protective mechanism against oxidative stress in cardiovascular patients [29]. Apparently, the production of superoxide and hydrogen peroxide in the patients under study has caused the decrease of GPx and SOD enzymes activity. Galle et al. reported that GPx has more dominance in deleting radicals in erythrocytes [30]. Moreover, the decrease of SOD enzyme activity may be due to lack of enzymes activity in connection with their depletion owing to peroxidation. The decrease of superoxide contents leads to the increase of SOD enzyme activity. Conversely, the increase of the contents of superoxide stops its activity. The findings indicated that the contents of vitamins A, E and C in angina pectoris were less than the control group ( $p=0.001$ ).

Studies showed that there was a significant decrease in the contents of vitamins A, E and beta-carotene in patients with acute myocardial infarction as well as coronary artery disease [16]. Carotenoids may have more useful effects in a synergistic manner and with the effectiveness of other anti-oxidants and vitamins E and C [31]. Several studies recommend that consuming foods with carotenoid prevents atherosclerosis, although clinical studies have not offered any evidence for it. Beta-carotene in the diets together with the other natural carotene is natural [32]. Although vitamin E is a potential anti-oxidant by itself, when it is consumed with other anti-oxidants, especially vitamin C and beta-carotene, its effects is intensified by a large amount [33]. Vitamin E leads to reduction of adhesion of monocyte-endothelial cells in vitro environment that are in connection with the decrease of adhesion of molecules created by the oxidized LDL [34, 35].

The effect of vitamin E supplement on the increase of vitamin E of plasma and the decrease of oxidized LDL has been identified. The alpha-tocopherol plays an intermediary role in producing nitric acid in endothelial cells [35]. Shortage of vitamin C and the decrease of ascorbic acid of plasma have been known as the risk factors for coronary artery disease [23]. The decrease of vitamin C contents of serum may be in connection with depletion of vitamin C to reduce or protect vitamin E from the damages of free radicals. In addition, scavenger antioxidants are important, not only due to the direct reaction with the free radicals, but also due to the increase of the effect of other antioxidants in a synergistic manner [36].

Two systems of enzymatic and non-enzymatic anti-oxidants reinforce the defense system because of the

intensification of the anti-oxidant effects. The intensification of one of the systems is by far less than the time when both systems work together. The decrease of TAC in the patients under study, concurrent with the increase of malondialdehyde, indicates the vulnerability of their anti-oxidant system. It was observed in the negative and significant connection with TAC and MDA and the positive and significant connection with vitamin C and SOD.

Studies indicate that low plasma level of vitamins A, E, C and beta-carotene follow the increase of lipid peroxidation and the risk of coronary artery diseases [37]. The active factors of oxygen cause damages to different tissues of body, including lipids, which follows the increase of oxidase activity and causes damages to heart tissues. The reverse and significant relationship between malondialdehyde and TAC indicates the increase of active factors of oxygen in the patients under study. The results of the research specified that with the significant decrease of enzymatic and non-enzymatic antioxidants and the activity of TAC of body and the increase of lipid peroxidation, the patients under study are subject to risk, mostly in the form of chronic angina pectoris.

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With respect to the relationship between oxidant and anti-oxidant indices, it seems that oxidative stress affects the antioxidant status of plasma on the patients under study and weakens that. However, the total antioxidant capacity of body is under the influence of different internal factors, including enzymes, uric acid and urate as well as the external factors including the intake diets and phytochemicals.

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#### Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

#### Conflict of Interest

The authors declare no conflict of interest.

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