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RESEARCH ARTICLE

Correlation of Myeloperoxidase Activity with Malondealdehyde Levels in Iraqi Patients with Coronary Artery Diseases

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Abstract

Background and Objective: Coronary Artery Disease (CAD) is one of the largest cause of mortality worldwide. The majority of CAD is caused by atherosclerosis, which is the main pathophysiological process underlying of CAD. The purpose of the current study was to investigate the role of myeloperoxidase (MPO) activity in coronary artery disease besides to its relationship with malondealdehyde levels, Athrogenic Index of Plasma (AIP) value and its association with the risk of future evolution of CAD in sera of Iraqi patients. Methods: Two main groups were included in this study; 60 patients (35male&25female) with coronary artery disease, and 40 (23male& 17female) apparently healthy controls comparable for age were enrolled in the current study. The blood samples were obtained for measurements of MPO activity, lipid profile, MDA levels and AIP value; for all participants. Results: The obtained results showed that there was a significant increases in serum MPO activity and MDA levels in coronary artery disease (46.35 ± 5.13 U/L) and (6.44 ± 1.32 nmol/ml) as compared with the control (29.12 ± 4.88 U/L) and (2.75 ± 0.43 nmol/ml), respectively. Meanwhile a highly significant increase in AIP value in CAD patients group in comparison to control group (0.36 ± 0.08, 0.076 ± 0.04), respectively. The activity of MPO was significantly correlated with MDA levels (r=0.751, p=0.000) and AIP value (r=0.762, p=0.000). Conclusion: According to the obtained results, MPO activity, levels of MDA and AIP value were elevated in patients with CAD. It can be concluded that higher MPO activity and its correlation with high MDA levels and AIP value may be associated with complications of CAD in the Iraqi patients.

Keywords: *Coronary Artery Diseases, Myelopreoxidase, Lipid peroxidation, Atherogenic Index of Plasma.*

Introduction

Oxidative stress and inflammation play the main role in the initial and progression of atherosclerosis plaques and development of cardiovascular artery disease (CAD) [1, 2]. A useful benefit for a high density lipoprotein (HDL) by reverse cholesterol transport, protects from possibility occur coronary artery disease (CAD). Moreover, HDL has anti-inflammatory and antioxidative properties.

Neutrophils are the most abundant leukocyte in humans which are among the first white cells recruited to infected tissues. Against certain pathogens like bacteria and fungi, neutrophils plays an important roles in host defense. Therefore, they exhibit a potent activity of microbicidal via generation of reactive oxygen species (ROS) [3, 5]. Atherosclerosis is an inflammatory disease, and the association of inflammation with the initiation and progression of atherosclerosis suggests that the marker of inflammation [C-reactive protein (CRP)], may be useful in predicting an increased risk of coronary heart disease (CHD) [6, 7]. Myeloperoxidase (MPO, E.C.1.11.2.2), a heme enzyme, is released in the europhilic granules of neutrophils, and to a lesser degree in the lysosomes of monocytes. MPO catalyzes the formation of reactive oxygen intermediates, in the presence of H_2O_2 and a halide ions (CL^-) forming hypochlorous acid (HOCl), (a powerful oxidant which is used to kill internalized bacteria and other pathogens) [8,9].

The classic model about MPO, is an oxidative enzyme having antimicrobial activity of the intracellular system of phagocytes. So, indicated it as host defense against invading microorganisms and part of an important

innate immune system [10, 11]. Neutrophils degranulation, disease situations, leads to a redistribution of MPO into extracellular, and it can oxidize halide ions as well as other substrates to mediate tissue damage and pathogenesis of several inflammatory diseases such as: such as neurodegenerative diseases and atherosclerosis [11]. In studies recently, have given attention to myeloperoxidase (MPO), one of innate immune system enzymes, as a potential CAD marker and a target for treatment [12].

The MPO activity diminishes nitric oxide bioavailability, which leads to endothelial dysfunction [13-15]. This combination of detrimental effects has culminated in the concept that MPO may be an active mediator of atherogenesis [12]. Indeed, the higher levels of MPO in patients with (CAD), can foretell future cardiovascular conditions in these patients and other patients with chest pain; even after adjustment for traditional risk factors [16-18].

Therefore, in most of these clinical studies, blood samples were gained in an acute status or when overt present of CAD. This may have influenced substantially the levels of MPO. Until now, the data amongst individuals who free from heart disease are absent. MPO caused increased oxidative stress, which mean imbalance between oxidant and antioxidant as a result the lipid peroxidation level is increased [19].

Malondealdehyde (MDA) is the most important studied product as a result of peroxidation of unsaturated fatty acids. MDA is considered to be the most important biochemical marker for determining the lipid peroxidation. Moreover, the reaction between MDA and proteins is highlighted in atherosclerosis, this is a major cause of CHD and strokes, which have clinical relevance [20].

Atherogenic index of plasma (AIP) is the novel indicator involved in atherogenicity. AIP value is linked directly to the risk of atherosclerotic as a result development of Cardiovascular Disease, which is acquired by [21]: {logarithmic transformation of the number found by: dividing Triglycerides (TG) value to HDL value}. Therefore the aim of the current project is to study the role of MPO activity and its link with MDA levels and AIP value present in CAD patients.

Material and Method

Chemicals

All chemicals and reagents (annular grade) were used without further purification.

Subjects

The study was carried out on a total number of 100 subjects, 60 patients were diagnosed with CAD (35 males & 25females) and 40 healthy persons (23 males &17 females) as controls. The patients whose age (56.61 ± 9.41 years) were diagnosed as having CAD and based on previous medical reports, laboratory tests and clinical examination by consultant cardiologist as well as had a positive C-Reactive Protein (CRP). They attended from teaching center in Iraq Baghdad (Ibn Al-Bitar Center for Cardiac Surgery) for the period from September 2018 to December 2018. The Ethics Committee of College of Science, University of Baghdad has approved the study protocol.

Fourty (40) healthy controls were enrolled, whose ages extended (52.48 ± 9.86) years and they were considered healthy, according to their history, without a past filled with coronary illness and not suffering diabetes or hypertension. Demographic and clinical data of patients and control groups were collected in the form of age, sex, weight, height and their health history. The body mass index (BMI) was measured as {weight in kilogram / height in meter square} [22].

The Exclusion Criteria

- Alcoholism and smoking
- Pregnancy
- The use of antioxidant supplements
- Kidney and liver diseases
- Rheumatoid arthritis
- Patients after surgery and other diseases that may be interfering with this study.

Blood Samples

Approximately 10 ml of venous blood was drawn from each interested after fasting for 8-12 hs, using 10 ml disposable syringe. The blood samples were taken from (8:30 to 11.30 a.m.) in plane tube and left for a 15 minutes at room temperature. Then, the sera were

separated, aliquoted and stored at -20◦C until use.

Determination of Serum MPO Activity

MPO activity in serum was determined according to Klebanoff and Clark [23]. The method was based on kinetic measurement of oxidation of *o*-dianisidine with MPO in the presence of hydrogen peroxide (H_2O_2) at 460 nm, resulting yellowish-orange product. One unit of MPO was defined as: degrading (1 µmol) of H_2O_2 per min at 25°C. Molar extinction coefficient (1.3×10^4 M^{-1} cm^{-1}) of oxidized *o*-dianisidine was used for the calculation. The MPO activity was expressed as U/L.

Determination of MDA Levels

MDA concentration was measured in the serum by precipitation method using thiobarbituric acid (TBA) as active substance [24]. The absorbance of the supernatant was measured at 532nm. The results of MDA expressed by nmol/ml.

Determination of Lipid Profile

Lipid profile: Total cholesterol (TC); Triglyceride (TG) and High density lipoprotein-cholesterol (HDL-C) levels were estimated by using commercial kit (Linear chemicals, Spain), while Low density lipoprotein-cholesterol (LDL-C) and the levels of Very Low density lipoprotein (VLDL) were determined by using Friedwald's formula [25].

Protein Determination

The total protein content was determined by using the available commercially assay kit (Linear Chemicals, Spain).

Atherogenic Index of Plasma (AIP) Determination

AIP was calculated by using the following formula: log (TG/HDL-C) [26] or it can be calculated by using an AIP calculator (www.biomed.cas.cz/fgu/aip/calculator.php). It can be classified according to the values obtained as: <0.1 associated with lower, between (0.1-0.24) associated with intermediate and more than 0.24 for high risk of CVD [27].

Statistical Analysis

The data were analyzed statistically by using SPSS software version 20. The results in this study were reported as a mean value ± standard deviation (SD) by using independent-samples t-Test to compare mean and Pearson correlation. The differences were considered as highly significant when ($p<0.001$), significant when ($p<0.05$) and non-significant when ($p>0.05$).

Results

Age, Gender and BMI

The demographic parameters of CAD patients and controls are illustrated in Table 1. The results showed that there was a significant differences ($p<0.05$) in age between CAD (56.61±9.41 years) and control group (52.48±9.86 years). In contrast with this, there were no significant differences between CAD and control groups with respect to gender ($p>0.05$).

The percentage of males in CAD and control was (58.3%, 57.5%) respectively, while the percentage of females was (41.7% , 42.5%) respectively as shown in Table 1, which mentioned that there was a non association between gender and the studied groups. Also, the results showed a high significant difference in BMI ($P<0.0001$) between CAD and control group 26.89±3.28 and 30.22±3.58 Kg/m^2, respectively.

Table 1: The age, gender and BMI of CAD and control groups

Groups	n	Age (years)	Gender		BMI (Kg/m^2)
			Male No. (%)	Female No. (%)	
Control	40	52.48±9.86	23 (57.5%)	17 (42.5%)	26.89±3.28
CAD	60	56.61±9.41 *	35 (58.3%)	25 (41.7%)	30.22±3.58 **

Note: *p<0.05 ; **p<0.001

Lipid Profile in CAD and Control Groups

The mean ± SD of the Lipid profile (TC, TG, HDL-C, LDL-C and VLDL) levels in control and CAD were illustrated in the Table 2. Serum total cholesterol (TC), TG and VLDL were significantly higher in the CAD group than control group while the CAD patients reported to have significantly lower HDL-C

as opposed to healthy control. Meanwhile, there were no significant differences in low density lipoprotein cholesterol (LDL-C) between the two groups (p>0.05).

Table 2: The lipid profile of CAD and control groups

Parameters	Control group n=40	CAD group n=60	*p*-value
TC mg/dl	174.87 ± 12.25	182.01 ± 16.75	0.016*
TG mg/dl	118.40 ± 18.82	186.68 ± 19.94	<0.0001**
HDL-C mg/dl	46.73 ± 5.50	36.88 ± 5.54	<0.0001**
LDL-C mg/dl	103.84 ± 13.79	107.74 ± 16.11	0.198
VLDL mg/dl	24.33 ± 6.06	37.28 ± 4.0	<0.0001**

Note: *p<0.05 ; **p<0.001

MPO activity and Specific activity in CAD and Control Groups

Serum MPO activity was significantly higher (p<0.001) the CAD patients than control (46.35±5.13, 29.12± 4.88 U/L, respectively), as shown in Figure 1. The mean ± SD of total protein (TP) in control (7.708±0.38 g/dl) and CAD patients (6.894±0.60 g/dl) showed significant decreased in TP in CAD patients compared to control, while the specific activity of MPO were significantly higher (p<0.001) in CAD patients compared to control group (0.678±0.12 and 0.377±0.07 U/g, respectively) (Table 3).

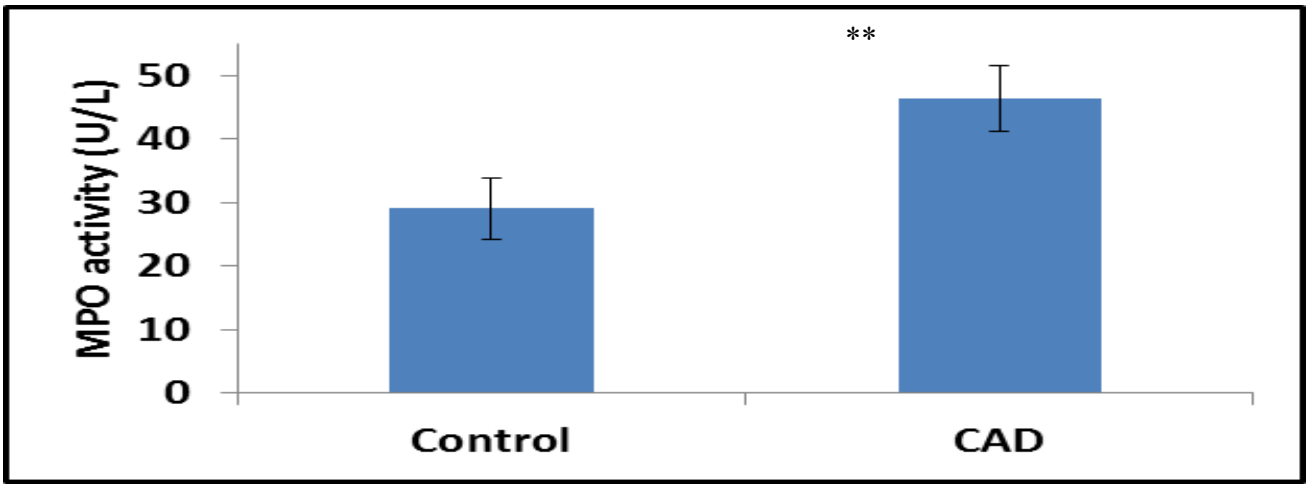

Figure 1: The MPO activity in CAD and control groups Note: *p<0.05 ; **p<0.001

MDA and AIP Value in CAD and Control Subjects

As mentioned in Table 3, there was a significant increase in the MDA levels in CAD patients (6.44 ± 1.32 nmol/ml) as compared to controls (2.75 ± 0.43 nmol/ml). Furthermore, the AIP value was significantly higher in CAD patients than control (0.36 ± 0.08 and 0.076±0.04, respectively).

Table 3: MPO, total protein, Specific activity, MDA and AIP of in the CAD and control subjects

Parameters	Control group n=40	CAD group n=60	*p*-value
MPO activity (U/L)	29.12± 4.88	46.35 ±5.13	<0.0001**
Total protein (g/dl)	7.708±0.38	6.894±0.60	<0.0001**
MPO Sp.activity (U/g)	0.377 ± 0.07	0.678 ± 0.12	<0.0001**
MDA nmol/ml	2.75 ±0.43	6.44 ± 1.32	<0.0001**
AIP	0.076±0.04	0.36 ± 0.08	<0.0001**

Note: *p<0.05 ; **p<0.001

Correlation of MPO with Other Parameters

Table 4 shows the correlation analysis between MPO and MDA, TC, TG, LDL-C, HDL-C, VLDL & AIP in both groups. Serum MPO activity were found to be significantly correlated with MDA levels (r= 0.751) and AIP value (r=0.762), as shown in Figure 2 (a&b respectively).

Table 4: Correlation of MPO with other parameters

Parameters	Pearson's correlation coefficient (r-value)						
	MDA	TC	TG	LDL-C	HDL-C	VLDL	AIP
MPO activity	0.751**	0.270**	0.722**	0.190	- 0.520**	0.648**	0.762**

Note: *p<0.05 and **p<0.01

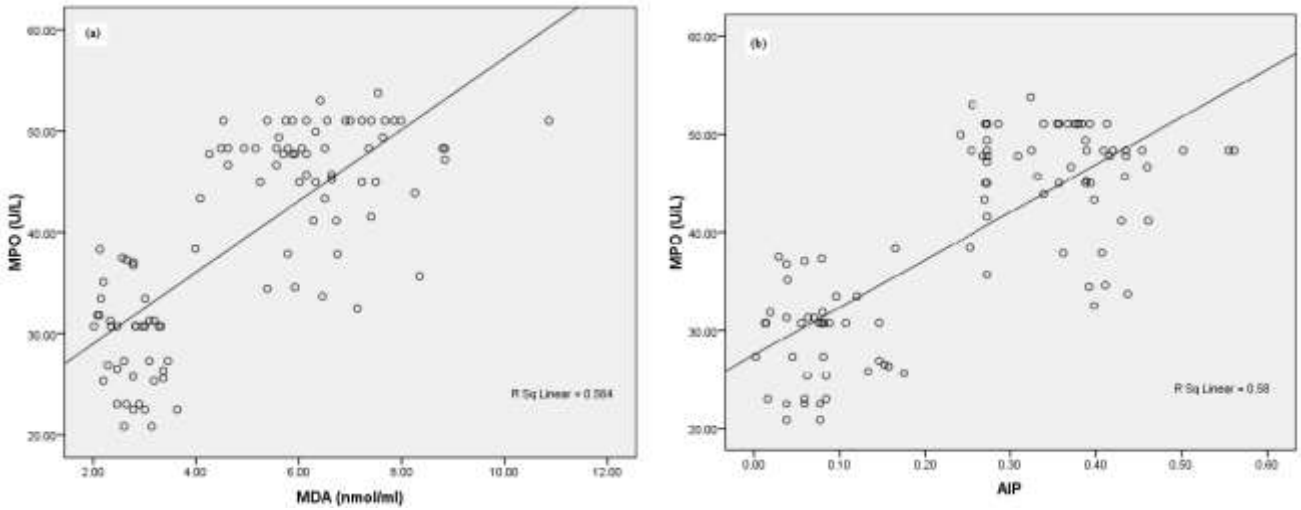

Figure 2: Correlation of MPO activity with (a) MDA level and (b) AIP value

Discussion

Myeloperoxidase has been involved in atherosclerosis, as a participant, through the mechanisms attached to its inflammation role such as: LDL oxidation and nitric oxide consumption leading to endothelial dysfunction [14,28,29]. MPO also may play a pathogenesis role in the acute coronary syndromes via plaque destabilization [29] thus several studies support possibility links between the MPO and the development of CAD. During acute coronary syndromes, circulating leukocytes release MPO [30].

Our results indicated that MPO activity was increased significantly in CAD group than control group (p<0.0001). Meanwhile, our present results are in agreement with those previous studies that deals with MPO in CAD [18,31]. This increased in MPO activity was hunched MPO and serves as an early inflammation marker, vulnerability of plaque and one that can be used to identify patients at imminent risk for major adverse cardiac events.

Through the activity of MPO, reactive oxygen species generated leads to an imbalance between oxidant and antioxidant molecules, this process called oxidative stress [32,33]. MPO produced an array of diffusible oxidants which is capable of initiating lipid peroxidation [34,35]. Sense, the cell membrane is rich in polyunsaturated lipids that are susceptible to oxidation by reactive oxygen species. MDA, which is used as an index of oxidative damage, is a product of auto oxidation decomposition of polyunsaturated fatty acids. Thus, high MDA concentration in patients indicated the increased lipid peroxidation in membrane [36]. However, enhanced lipid peroxidation may occur as a result of the fact that suppression of naturally occurring scavenging mechanisms and enhanced the free radical generation processes [37]. In our present study, the MDA levels increased significantly in CAD patients comparing to control group (p<0.001). This findings are compatible to other authors who reported increased concentration of MDA in CAD patients [38].

In addition, the present study showed a positive correlation between the MPO and MDA, this indicated that the increase of MPO activity in patients with CAD leads to increase free radical that attached polyunsaturated fatty acid as a result, then increasing the lipid peroxidation due to increasing the concentration of MDA. Moreover, hyperlipidemia {specially hypertriglycermia} can lead to increase in lipid peroxidation [39]. There are many variables contribute to CHD risk, such as plasma lipid profile [TC, TGs, LDL, and HDL].

The results of this study showed that the patients had abnormal lipid profiles when compared to the controls, where the TGs, TC and VLDL were significantly increased in patients than control groups, and HDL-C was significantly lower in patients than control while LDL-C show non significant between

each groups. Similar observations was found in previous studies who reported an abnormal lipid profile in CHD cases [40]. Gaziano *et al.* [41] reported that the ratio of triglycerides to HDL was a strong predictor of myocardial infarction. Furthermore, elevation in triglycerides increases CHD risk, but its effect can be counteracted by the levels of HDL-C [42]. Interestingly, in this study, the correlation between MPO and lipid profile was found.

These findings means that the correlation between MPO activity and abnormal lipid profile could be established as a risk factors in the pathomechanism of atherogenesis and cardiac diseases. The atherogenic index of plasma been successfully used as an additional index when assessing cardiovascular (CV) risk factors [43, 44]. The calculating results of AIP value for patients show a higher than control group this means a higher risk for cardiovascular disease. The value of AIP below (0.1) considerable low risk of CVD and (0.1 - 0.24) medium risk as well as above (0.24) high CVD risk [45]. Anyhow, it has been indicated that AIP value has higher predicted to atherosclerosis. Likewise, some ratio of pro-atherogenic markers when divided by HDL-c, will increase the odds ratio value which mean higher predictive toward atherosclerosis, as oposed to pro-atherogenic markers alone [46].

The correlation analysis was also represented graphically by scatter diagram. In this study, MPO activity possitively correlated with AIP.

Conclusion

According to results found in this study, MPO activity and MDA levels as well as AIP value increased in Iraqi patients with coronary artery disease. Moreover, our findings indicated that the elevated in MPO activity was associated with increased of MDA levels and AIP that may contribute to complications and mortality of CAD in the Iraqi patients.

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