Original Article

# Myeloperoxidase levels predicts angiographic severity of coronary artery disease in patients with chronic stable angina

Mehdi Baseri, Ramin Heidari, Behzad Mahaki[1], Yaghoub Hajizadeh[2], Amir Momenizadeh, Masoumeh Sadeghi[3]

Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, [1]Department of Biostatistics, Isfahan University of Medical Sciences, [2]Environment Research Center, Isfahan University of Medical Sciences, [3]Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

## Abstract

**Background:** Myeloperoxidase (MPO) has an important role in the both processes of inflammation and oxidative stress. It plays proatherogenic role via low-density lipoprotein oxidation, functional inactivation of the high-density lipoprotein and endothelial dysfunction, and seems to be involved in the atherogenesis of coronary arteries. This study designed to evaluate the association between the plasma MPO levels and angiographic severity of coronary artery disease (CAD) in patients with the stable CAD.

**Materials and Methods:** Sixty-eight patients who had documented CAD with angiography and 66 subjects who had normal angiography were selected as case and the control groups for this study, respectively. Gensini scoring system was used for evaluation of severity of coronary artery stenosis. Plasma MPO and C-reactiveprotein (CRP) levels of both case and control groups were determined.

**Results:** Plasma MPO levels and CRP levels were significantly higher in CAD patients ($P < 0.001$), and plasma levels of MPO and CRP were correlated with Genssini scores.

**Conclusions:** Our findings indicated that the plasma MPO levels increase in patients with stable CAD and hence that, it can be used as adiagnostic factor to predict the coronary artery atherosclerosis severity in stable CAD patients; However, it needs further widespread investigations to achieve an accurate cut point.

**Key Words:** Angiography, coronary artery disease, C-reactiveproteine, myeloperoxidase

**Address for correspondence:**
Prof. Massoumeh Sadeghi, Cardiac Rehabililitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: sadeghimasoumeh@gmail.com

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## INTRODUCTION

In the way of atherosclerotic plaque formation, inflammation and inflammatory biomarkers and process have been involved at all stages, from the initial development of endothelial dysfunction, through to the formation of the established atheroma and its subsequent rupture.[1]

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Myeloperoxidase (MPO) is secreted by activated neutrophils and macrophages, and has been known as inflammatory biomarker.[2] MPO has been associated as a noticeable contributor to the process of progress, propagation and complication of atherosclerosis.[3,4] The enzyme and products of MPO catalyzed oxidation reactions (tyrosylation, nitration, and halogenation) have been recognized



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in human atherosclerotic lesions, further proposing that MPO may show a pathophysiological part in atherogenesis.[5] Several mechanisms may describe the proatherogenic role of the MPO, such as low-densitylipoprote in (LDL) oxidation and creation of foam cells, functional inactivation oft he high-densitylipoprotein (HDL), endothelial dysfunction due to reduction of nitricoxide bioavailability, activation of metalloproteinase 7, and rise in the vascular cell apoptosis, which result in endothelial erosion and plaque vulnerability.[5-10]

Inflammation and oxidative stress are linked with atherosclerosis. MPO is linked to both processes inflammation and oxidative stress via its release by leukocytes and its character in catalyzing the creation of oxidizing agents. Recent studies have underlined the importance of the MPO for cardiovascular disease.[11,12] MPO levels are higher in patients with the coronary artery disease[12], and it has been found to predict cardiovascular disease progress.[12,13] Serum MPO levels help as a powerful and independent interpreter of endothelial dysfunction in human subjects. MPO mediated endothelia ldysfunction may be a significant mechanistic relation between inflammation, oxidation, and cardiovascular disease.[9] Furthermore, MPO has been stated to play a role in plaque vulnerability.[7] Oxidative stress biomarkers that recognize in stability in the coronary artery plaque (such as MPO) may be valuable for screening patients with the stable CAD who are under extreme risk and may need more aggressive treatment.

This study is designed to assess a likely relation between the plasma levels of MPO and the severity and extent of CAD documented byangiography.

## MATERIALS AND METHODS

### Study design and population

The study protocol was accepted by the department of cardiology of Isfahan University of Medical Science. The ethical acceptance for the study was provided by the institutional ethics committee.

The population study were those had the clinical features of stable CAD, and stable angina diagnosis considered for them by a cardiologist and they were enrolled for elective diagnostic coronary angiography at Noor Hospital and Shahid Chamran Hospital (Isfahan University of Medical Science, Iran) between April 2011 and September 2011.

A total of 68 patients who had CAD documented by angiography were selected randomly among populations tudy as a case group and 66 subjects who had normal angiography were selected as a control group. The age, sex, and smoking variables were matched within the case and control groups.

Exclusion criteria for this study was: 1-Acutecorona rysyndrome 2-Prior Coronary artery bypass grapht (CABG) 3-Prior angioplasty 4-Chronic renal failure 5-Inflammatory and infective disease 6-History of malignancy, radiotherapy and chemotherapy 6-Sever valvular disease 7-diabetes mellitus.

The patients'clinical data were recorded including acknowledged coronary risk-factors such as age, weight, height, waist, smoking and Hypertension (HTN).

### Definition

Systemic hypertension was defined in-patients who take antihypertensive medication or patients with a systolic blood pressure of > 140 mmHg and/or diastolic blood pressure of > 90 mmHg on at least 2 separate times. Diabetes mellitus was defined in patients who take insulin or oral hypoglycemic medication. For other patients screening by fasting blood glucose test was performed.

### Biochemical methods

All patients have gone under diagnostic coronary angiography. After femoral sheath inserted and before catheterization 10ml of bloods amples were drawn and transferred into EDTA-tube, centrifuged immediately at 4,000 rpmfor 10 min in a cold centrifuge, and plasma aliquots were stored at −80°C until analyses were performed. Plasma MPO level was determined with an ELISA assay kit (Immunology Consultants Laboratory, Inc., Newberg, OR, USA). Plasma total lipoproteinprofile (total cholesterol, triglycerides, LDLcholesterol, and HDL cholesterol) were determined using the standard enzymatickits (Parsazmun, Tehran, Iran). Plasma levels of hsC-reactive protein (CRP) were measured with a latex-enhanced immune turbidometric assay (Roche Diagnostics, Germany).

### Angiographice valuation

All the patients'angiograms reviewed by two interventional cardiologists who were unaware of the scheduled patients'data and their MPO plasma levels.

Quantitative coronary angiography was performed using an automated edge detection system (SIEMENS). Genssini scoring system was applied for determining the extent and severity of coronary artery stenosis and to reveal the extent of coronary atherosclerosis. The genssini scores points were from 0 to 400.

### Statistics

Continuous variables were expressed as mean ± standard deviation. Furthermore, for categorical variables, frequencies and percent were reported.

According to the results achieved by the Kolmogrov Smirnov test, Mann–Whitney u test, and Chi-squared test were used to assess the variables between the case and the control groups. Multiple regression analysis was applied to assess the relationship between the genssini scores and CRP, HDL, MPO variables in case (CAD) group. All analyses performed using the SPSS 16.0 $P < 0.05$ were considered as significant.

## RESULTS

The demographic and baseline characteristics of the populations studied are described in Table 1. In addition, to compare the continuous and discrete variables in two groups, Mann–Whitney u test and Chi-squared test were carried out respectively, which are also shown in Table 1.

These statistical tests clearly show that the sex, age and smoking habits of both study groups are well matched with $P$ values of 0.36, 0.47 and 0.59, respectively as mentioned in the study methods.

Plasma levels of HDL were significantly higher in the control group than who had CAD ($P < 0.001$); however, according to the results from multiple regression in Table 2, nosignificant correlation was seen between HDL and genssini scores ($P = 0.57$).

Plasma concentrations of MPO were significantly higher in the CAD (stenosis showed angiographically) than the control group [median 44.00(24-93) and median 34.74(15-54) respectively; $P < 0.001$] [Figure 1] and also significant association was observed between MPO levels and genssini scores ($P < 0.001$) [Table 2].

Plasma levels of CRP were significantly lower in the control group than CAD group (4.07 ± 0.617; 5.15 ± 1.48 respectively; $P < 0.001$), and also there was a significant correlation between the CRP and genssini scores ($P = 0.022$) [Table 2].

**Table 1: Baseline demographic, clinical and biochemical characteristics of subjects with and without CAD**

| Variables | CAD *N*=68 | Non CAD *N*=66 | *P* value |
|---|---|---|---|
| Gender (male) | 49 (72) | 40 (61) | 0.36 |
| Age | 62.44±9.42 | 60.86±10.69 | 0.475 |
| Totalcholesterol (mg/dl) | 175.24±39.14 | 168.09±32.47 | 0.659 |
| HDL (mg/dl) | 40.90±8.13 | 51.05±9.398 | <0.001 |
| LDL (mg/dl) | 100.31±25.66 | 91.18±26.04 | 0.182 |
| TG (mg/dl) | 144.59±57.21 | 137.50±53.35 | 0.679 |
| T.Ch/HDL | 4.39±1.06 | 3.347±0.69 | <0.001 |
| HTN (mmHg) | 35 (51.1) | 5 (22.7) | 0.019 |
| Smoking | 32 (47) | 28 (42) | 0.59 |
| BMI (kg/m$^2$) | 27.99±3.23 | 26.9±4.68 | 0.143 |
| CRP(μg/ml) | 5.15±1.48 | 4.07±0.617 | <0.001 |
| Myeloperoxidase (ng/mL) | 44.00 (24-93) | 34.74 (15-54) | <0.001 |

CAD: Coronary artery disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerides, T.Ch: Total cholestrol, HTN: Hypertension, Results are expressed as number (percentages) or means±SD

## DISCUSSION

MPO has been involved in atherosclerosis through mechanisms related to its role in inflammation.[5,14] Inflammatory events have been involved at all stages in the progress of atherosclerotic plaque, from the initial development of endothelial dysfunction, through to the formation of the established atheroma, and its subsequent rupture.[1] Macrophages have a key role in lesion creation and evolution, raising the possibility that these inflammatory cells might be a main source of oxidants that damage HDL in the artery wall. One potential way includes reactive intermediates made by MPO, a heme enzyme produced at high levels by macrophages in the arterywall.[15] Human atherosclerotic lesions is enhanced by multiple oxidation products of LDL formed specifically by MPO, such as chlorotyrosine[16] and Schiff base adducts of p-hydroxyphenyl-acetaldehyde (atyrosineoxidation).[17] Oxidation of apolipoproteinA-I (apoA-I) by MPO has been proposed to deprive HDL of its cardioprotective effects. Tyrosine 192 is the main site of chlorination in apoA-I in both plasma and lesion HDL isolated from humans. Chlorination of apoA-I by MPO creates a dysfunctional form of HDL.[18] MPO also may has a role through enhancing endothelial dysfunctionin CAD patient.[19] It diminishes nitric oxide related smooth muscle relaxation[20] and MPO decreases nitricoxide mediated vasorelaxant replies.[19] Recent evidence suggests that MPO activeity precipitates atherogenesis. Several studies support potential links between the MPO and the development of CAD.

In our study, patients with the CAD had upper plasma MPO levels than control groups, and there

**Table 2: Results of multiple regression analysis to test the relationship between genssini scores and MPO, CRP, HDL variables in coronary artery disease patients**

| Variables | Genssiniascore | | *P* value |
|---|---|---|---|
| | Coefficient (95%CI)* | SE** | |
| Plasma MPO | 0.276 (0.583-1.883) | 0.102 | <0.001 |
| Plasma CRP | 0.172 (3.502-21.457) | 0.07 | 0.007 |
| Serum HDL | −0.159 (−6.733-3.138) | 0.062 | 0.471 |

MPO: Myeloperoxidase, CRP: C-reactive protein, HDL: High-density lipoprotein, CI: Confidence interval, *Coefficient of the multiple regression and 95% confidence interval, **Standard errors of the coefficient

were significant differences in MPO levels between two groups.

In a previous study, a correlation between systemic MPO levels and the level of stenosis in major coronary arteries has been shown.[12] MPO levels are associated with the presence of angiographically proven coronary atherosclerosis.[12,21]

This association was studied by Düzgünçinar *et al*.[22] A relation was observed for MPO plasma levels and extension of CAD by Wainstein *et al*.[21]

Baldus *et al*. observed that MPO plasma levels were higher in patients with the CAD compared to a control group, although, the difference between two groups was not significant.[23]

In a study by A daStefanescu *et al.*on 382 patients elevated plasma MPO concentration was associated with a more advanced cardiovascular risk profile.[24] however, In a study on 557 patients by Kubala *et al.* the authors have found that MPO levels did not differ significantly between patients with and without CAD.[25]

Furthermore, in our study, MPO level showed a significant correlation with genssini scores either, this evidence can implicate a significant role of MPO in the pathogenesis of coronary atherosclerosis. Hence that MPO can be considered as independent risk-factor for CAD.

HDL normally defends against atherosclerosis by eliminating excess cholesterol from macrophages in the vascularwall, a process named reverse cholesterol transport.[26] Strong reverse relationship between HDL cholesterol and the coronary heart disease.[27] Ametaanalysis off our prospective studies (theFraminghamHeartStudy, the Multiple Risk-Factor InterventionTrial, the Lipid Research Clinics Prevalence Mortality Follow up Study and the Coronary Primary Prevention Trial) revealed that every 1 mg/dl (0.026 mmol/l) rise in HDL cholesterol is associated with a significant coronary disease risk reduction of 2% in men and 3% in women.[28] Patients with angiographically proven CAD more often have low levels of HDL.[29] The process of reverse cholesterol transport may explain protective role of HDL against coronary disease. HDL can also carry antioxidant enzymes that may reduce the levels of oxidizd phospholipids in atheromatous lesions, which could enhance atherogenesis.[27-29] In the present study, patients with CAD had lower HDL plasma levels than the control group; however, no relationship between HDL and genssiniscores was observed. Furthermore, total cholesterol/HDL ratio was lower in the control group. Inflammation and infection can deprive HDL of its cardioprotective effects and HDL becomes prooxidant.[30,31] Several inflammatory markers were related with an increased Coronary artery disease (CHD) risk, independent of traditional CHD risk factors.[32] In our study, CRP plasma concentration was higher in the case group and significant relationship was found between CRP levels and genssini scores. These relationships between inflammatory biomarkers MPO, CRP, and CAD patients in this study can implicate the importance and the role of inflammation in development of atherosclerosis and CAD. Brennan *et al*. reported that a single determination of plasma MPO independently predicts the risk of myocardial infarction, in addition to the risk of major adverse cardiac events in the 1month and 6-monthperiods[11] and elevated level of MPO were independently related with increased risk of CHDevents.[33] Plasma MPO level can use as independent prognostic predictor for long term incident major adverse cardiovascular event in stable CAD patients followed medically.[34] Heslop *et al*. stated that MPO accurately predicts cardiovascular mortality risk in the CAD patients documented by angiography and considering MPO and CRP together may improve long term risk assessment of CAD patients outcomes.[35] MPO deficiency (a genetic disease) is related with a decreased prevalence of cardiovascular events.[36] A mutation in the MPO gene, which results in reduced enzyme expression was reported to be associated with the diminished risk of CAD.[37] When several biomarkers compared to each other, elevated MPO concentration were found to be highly sensitive predictors of future cardiovascular events.[38,39]

## CONCLUSION

The results of the presents tudy show significantly higher levels of plasma MPO in angiographically documented CAD than healthy individuals, and MPO can reflect the extent and burden of coronary artery atherosclerosis in stable CAD patients. As regards, other articles that state association between MPO levels and future cardiovascular events in CAD,[32-35] MPO can beused as diagnostic and prognostic factors, and measurement of MPO may be used as an independent factor for risk stratificationin CAD patients. However, this aim entails future studies with a larger participants in order to determine accurate cut point value in CAD patients and healthy population.

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