



ORIGINAL ARTICLE

Correlation of Fibrinolysis Marker of Plasma Plasminogen Activator Inhibitor type-1 and Oxidative Stress Parameters in Occurrence and Progression of coronary Artery Disease

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ABSTRACT

Coronary artery disease (CAD) is a leading cause of death of women and men worldwide. Fibrinolysis and oxidative stress may be considered as novel risk factors of coronary artery disease (CAD). In the present study we made an attempt to evaluate the association between plasminogen activator inhibitor type-1 (PAI-1) as a fibrinolysis marker and oxidative stress status parameters [malonaldehyde (MDA), and oxidized low density lipoprotein (ox-LDL)] and also their association with progression of CAD. Besides general risk factors, PAI-1, MDA and ox-LDL were compared between 160 angiographically diagnosed CAD patients and 20 age/sex matched healthy subjects. Furthermore, according to the number of occluded vessels CAD patients subdivided into 4 groups and association between all risk factors and severity of CAD was examined. Using multiple regression analysis independent correlation of MDA and ox-LDL with PAI-1 was revealed. Our findings showed that not only the levels of PAI-1 and oxidative stress parameters in CAD patients are significantly higher than controls, but there are a significant difference between the levels of these parameter among subgroups of patients who were divided based on the progression of CAD. According to our statistical analysis, an independent correlation was revealed between the PAI-1 and oxidative stress parameters. Findings from this study suggest that PAI-1, and oxidative stress parameters (ox-LDL and MDA) are mutually involved in the occurrence and progression of CAD and these parameters may be useful in diagnosis and monitoring of CAD in patients.

Key words: Coronary artery disease, MDA, ox-LDL, PAI-1.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death of women and men worldwide [1]. Many studies have conducted in various populations through the world, in order to understand the complex nature of CAD (2-4). As reviewed by Peter W.F.Wilson [5], long-standing risk factors for the development of CAD have typically included age, blood levels of total and high-density lipoprotein (HDL) cholesterol, blood pressure, cigarette use, diabetes mellitus, and left ventricular hypertrophy on electrocardiography [5]. In addition to traditional risk factors, lipoprotein metabolism abnormalities, oxidative stress, [6-8] and susceptibility to thrombosis [9] are considered as significant and novel risk factors for CAD.

Plasminogen activator inhibitor-1 (PAI-1), originating from vascular endothelium as well as platelets [10], is an important regulator of fibrinolysis [11] and its elevated serum activity is associated with the impairment of vascular wall and endothelial dysfunction. Elevated plasma PAI-1 activity was also related to the intima – media thickness of carotid arteries in a cross-sectional case – control study [12].

Oxidative stress may have an important role in pathogenesis of atherogenesis. Production of excessive reactive oxygen species in oxidative stress conditions results in prooxidation of polyunsaturated fatty acids which are of the main components of lipoproteins. Among lipoprotein, LDL comparably undergoes more lipid prooxidation [13, 14]. Elevated levels of oxidized LDL (Ox-LDL) have previously been detected in the plasma of CAD patients [15]. Oxidatively Ox-LDL penetrates into the artery wall at the earliest stage of atherosclerosis leads to generation of foam cells, as the main factor of atherosclerosis. It is also undergoes

further oxidative or enzymatic modifications. Ox-LDL and related compounds also are observed in lesion formation at the later stages of atherosclerosis. Therefore, Ox-LDL could play a role both in atherogenesis and in plaque complications [16, 17]. Malondialdehyde (MDA) is an index which is commonly used to evaluate the lipid peroxidation [18, 19]. Previous studies have confirmed the involvement of lipid peroxidation in CAD by referring to the significantly higher plasma levels of MDA observed in CAD patients compared with healthy controls [20-22].

To further understand the role of both oxidative stress and thrombosis and their inter-relationship in patients with CAD, we measured MDA, Ox-LDL and PAI-1 parameters in plasma of Iranian coronary artery disease patients.

MATERIALS AND METHODS

Subjects

In the present study 180 subjects consist of 160 patients with angiographically proven CAD have previously been described [23] and 20 age and sex - matched healthy controls were included. Blood samples were collected from the CAD patients recruited at the Cardiology Unit of the Shahid Madani hospital, Tabriz. The ethics committee of Tabriz University of Medical Sciences approved the study. Informed consent was obtained from all of the patients. None of the healthy subjects recruited reported any past heart problems, or had a family history of CAD. Subjects with the history of any heart disease, lung disorder liver dysfunction, renal disease and cancer were excluded from the study. The CAD population were divided into four groups according to the angiography results; CAD patients who suffered from chest pain like angina pectoris but with no occluded (V0), patients with one occluded vessel (V1), patients with 2 occluded vessels (V2), patients with 3 occluded patients (V3).

Blood sampling

Fasting venous blood samples (10 ml) were collected. Blood samples were centrifuged at 1500g for 10 minutes at room temperature within 1 hour after collection and stored at -70°C until the assays were performed.

Assays

Enzyme-linked immunosorbent assay (ELISA) procedures were used to determine the serum Ox-LDL (Glory Science co. Ltd Cat. No: 93614) and PAI-1 levels (Boster Science co. Ltd Cat. No: EK0859). Serum MDA was measured based on reaction with Thiobarbituric Acid (TBA), extraction conducted with normal butanol, absorption measured by spectrophotometer and value calculated according to a standard curve [24]. The assay was analyzed on semi-auto analyzer (Alcyon 300 made in USA) in the Biochemistry lab. Lipid profile and other biochemical parameters were measured with routine laboratory methods [25-27] with an automated chemical analyzer. The LDL-cholesterol level was calculated by Friedewald formula [28].

Statistical analysis

Data are presented as mean \pm SD. Statistical analysis was performed using SPSS version 16. Comparisons of continuous parameters were performed using the Student's t test or ANOVA where appropriate. χ^2 -test was used to examine the differences between categorical variables for contingency tables. Spearman's non-parametric correlation analysis or Pearson analysis were used (where appropriate) to assess associations between oxidative stress parameters (MDA and ox-LDL) or fibrinolysis parameter of PIA-1 and other studied variables and subsequent multiple regression analysis to estimate the independent contribution of predictors to the variance in plasma MDA, ox-LDL and PAI-1 levels. P values less than 0.05 were considered statistically significant.

RESULTS

Table 1 represents the general characteristics and biochemical parameters assessed in the study populations. As expected the CHD population had a higher percentage of diabetics, smokers and hypertensive subjects. TG concentration was significantly higher than control population. In contrast, the concentrations of HDL-C was lower in the CHD population than control population. The concentrations of t-Cholesterol and LDL-C were not of significant difference between two populations. This unexpected results and was most likely due to the dietary habits of all the participants in the present study.

Table 1. General characteristics and some basic biochemical parameters of the study populations.

Variable	Control	CAD	P value
Number	20	160	
Range	53-65	35-87	NS
Male (%)	85%	66%	NS
Hypertension N (%)	0 (0%)	84 (56%)	0.00
Smoker (%)	1 (5%)	82 (55%)	0.00
Diabetes mellitus, n (%)	0 (0%)	32 (21%)	0.02
Total cholesterol, mg/dL	183.5±10.7	191.5±6.2	NS
HDL cholesterol, mg/dL	37±1.1	33.4±0.8	0.04
Triglycerides, mg/dL	132±14.5	181.5±8.1	0.01
LDL cholesterol, mg/dL	120±11.5	121±5.3	NS
PAI-1 (ng/ml)	48.80±19.42	72.3±16	0.00
MDA(mmol/ml)	4.30±1.49	6.11±1.57	0.01
OX-LDL(ug/mL)	1.424±0.25	2.782±0.896	0.00

NS : non-significant

As table 2 indicates, regarding to the degree of CAD severity, CAD population were subdivided into 4 groups: 0: stenosis less than 50%, 1: stenosis of one vessel, 2: stenosis of two vessels and 3: stenosis of three vessels. Using one-way ANOVA, we did not find any difference in the level of TG, HDL-C, t-Cholesterol, LDL-C parameters between any of the 4 CAD groups, however for new factors including MDA, Ox-LDL and PAI-we observed a significantly different value between subdivided groups.

Table 2. Biochemical parameters among sub-groups of CAD patients which subdivided based on the number of occluded vessels according to the ANOVA.

Variable	0v	1v	2v	3vp	p
PAI-1 (ng/ml)	51.20±10.69	75.17±11.81	77.91±9.10	85.64±8.24	0.00
MDA(mmol/ml)	5.41±0.16	5.646±0.14	6.54±0.87	6.79±0.1	0.00
OX-LDL(ug/mL)	2.22±0.47	2.78±0.51	2.92±1.01	3.19±1.07	0.00
TG(mg/dL)	173.82±77	203.41±63	176.92±92	175.11±87	0.39
T-chl(mg/dL)	177.41±53	202.84±48	188.27±68	199.21±73	0.29
HDL (mg/dL)	33.84±7	34.09±6	31.97±9	34±8	0.61
LDL(mg/dL)	108.82±46	127.84±43	121.93±54	130.16±66	0.31

0V: stenosis in none of vessels, 1V : stenosis in one of vessels, 2V : stenosis in two of vessels, 3v: stenosis in three of vessels

Spearman's and Pearson (for nonparametric and parametric analysis, respectively) correlation analysis of the CAD population revealed that except for LDL and t- cholesterol which showed a positive significant ($p < 0.016$ and $p < 0.022$, respectively) correlation with PAI-1, there was observed no other significant correlation between traditional risk factors and new risk factors. Pearson correlation analysis conducted to explore the correlation between new risk factors of oxidative stress status and fibrinolysis marker of PAI-1. There were significantly positive correlations between oxidative stress parameters (ox- LDL and MDA) (0.00 and 0.017, respectively) and PAI-1, however the correlation between ox-LDL and MDA was not significant (data not shown).

Table3. Association between the plasma oxidative stress status parameters and the fibrinolysis parameter of PAI-1 in CAD patients according to multiple regression analysis

Parameters	B (β)		
	PAI-1	MDA	OX-LDL
PAI-1 (ng/ml)	- ^a	0.017 (0.180)*	0.018 (0.327)**
MDA(mmol/ml)	1.66 (0.162)*	-	-
OX-LDL(ug/mL)	5.82 (0.318)**	-	-

* $p = 0.038$, ** $p = 0.00$. a: Not included in the model.

In multiple regression analysis, ox- LDL and MDA were factors that showed an independent influence on plasma PAI-1 (table 3).

DISCUSSION

The role of oxidative stress as an important factor in the initiation and progression of atherogenesis has been comprehensively reviewed by Natalie A. Strobel *et al* [29]. Prognostic value of plasma fibrinolysis activation markers in cardiovascular diseases is also suggested in previous studies which is reviewed by Diana A. Gorog [30]. In the present study we made an attempt to examine the association between oxidative stress and thrombosis in an Iranian CAD population.

It is postulated that oxidative stress is primarily mediated through the oxidation of low-density lipoprotein (Ox-LDL) and that the oxidation of other molecules (lipid, protein, and DNA) are also involved [29]. Therefore, to evaluate the oxidative stress status in CAD patients we assessed the levels of MDA and Ox-LDL in patient's blood. The results from our study revealed elevated levels of both MDA and Ox-LDL in CAD patients compared to controls (table 1). Regarding to the extent of disease, CAD patients in this study were divided into four sub-groups, based on the number of occluded vessels, and in this way also we observed a significant association between oxidative stress status parameters (MDA and Ox-LDL) and the extent of CAD in patients (table 2). Our results confirm data from previous studies found lipid peroxidation could potentially be more sensitive and highly correlated to large stenotic vascular lesion changes. [31,32]. In contrast, Kotur-Stevuljevic *J et al* [33] Bridges *et al*. [34] and Stranger *et al* did not find any significant correlation between MDA [35] and the angiographic diagnosis that indicated the severity of CAD. In agreement with our findings the results from a prospective 3-year study show that circulating OxLDL is associated with the progression of ultrasound-assessed atherosclerosis in CAD patients [36]. In another study the titre of autoantibodies to Ox-LDL was introduced as an independent predictor of the progression of carotid atherosclerosis in Finnish men [37]. The similar conclusions were proposed by others [38 – 40].

Results from our study showed that PAI-1 is significantly elevated in CAD patients in comparison to controls and it has also a significant association with severity of the disease. Masanao, *N et al* (2007) reported that PAI-1 is an independent predictor of coronary microvascular dysfunction in hypertension [41]. Elevated levels of PAI-1 concentrations predict subsequent myocardial infarction unstable angina pectoris [42] and are associated with progressive coronary artery disease in young men with a history of myocardial infarction [43]. In addition, a genetic polymorphism in the promoter region of the PAI-1 gene which results in high plasma PAI-1 concentrations is associated with unstable angina [44]. Clinical studies indicate a correlation between occurrence of coronary artery disease, insulin resistance and high plasma PAI-1 concentrations [45-47]. Therefore, it is assumed that the increased expression of PAI-1 in blood vessels which results in localized alterations in fibrinolytic activity, may contribute to the progression of atherosclerotic process by promoting fibrin deposition and extracellular matrix accumulation in the lesions [48].

Data from our study showed that; although there are significant differences in the amounts of HDL and TG and also the incidence of smokers, hypertensive and diabetes subjects in CAD patients compared to controls, however except for smoking habit which had a higher percentage in patients, no correlative association observed between these traditional risk factors of CAD and the parameters of oxidative stress status or thrombosis. Our analysis also showed no correlation between none on traditional risk factors assessed in this study and progression on CAD.

Therefore, our results may suggest that although traditional risk factors examined in this study may involve in the initiation of the disease, but they are not associated with the progression of CAD in patients. We found that both oxidative stress parameters showed a positive correlation with fibrinolysis marker of PAI-1 examined in this study. Our data are in support of previous studies reported the association of hypercholesterolemia in humans with impaired fibrinolysis resulting from either reduced tissue-type plasminogen activator or enhanced PAI-1, which both of which also participate in the complication of atherosclerosis [49, 50]. In an experimental study conducted on mice, it was demonstrated that hypercholesterolemia enhanced daily expression of the PAI-1 genes in the mouse liver. Therefore, the risk or high frequency of acute atherothrombotic events still seems to be a factor that may be augmented under conditions of hypercholesterolemia [51].

Using multiple regression analysis, MDA and Ox-LDL remained in a statistically independent correlation with PAI-1, a result also obtained in a cross sectional study which provided the evidence of a close relationship between increased PAI-1 levels and urinary 8-iso-PGF_{2a} (an *in vivo* marker of oxidative stress), in android obesity [52], another study reported that Oxidative stress activates the plasminogen activator inhibitor type 1 (PAI-1) promoter through an AP-1 response element and cooperates with insulin for additive effects on PAI-1 transcription [53]. In one study conducted on mesangial cells authors concluded that Oxidized LDL activates PAI-1 transcription through autocrine activation of TGF- β signaling [54].

PAI-1 is involved in many physiologic and pathologic processes and its expression is affected by various growth factors, chemo-physical agents and cytokines. Oxidative stress (ROS/RNS) is believed to regulate PAI-1 gene expression through all these factors. Molecular pathways of MAPK and NF- κ B have been shown to be sensitive to redox statues and postulated to be the main downstream pathways whereby oxidative stress exerts its influence on PAI-1 expression [55].

CONCLUSION

In conclusion our findings may suggest that the CAD patients are in an exacerbated oxidative stress condition which is in close correlation with the extent of the CAD. Oxidative stress and molecules produced as a result of it, are involved in the consequential elevation of PAI-1 and the strong relationship between oxidative stress and fibrinolysis marker of PAI-1 revealed their mutual involvement in the progress of CAD. The precise mechanisms connect the inter relationship between the two process of oxidative stress and fibrinolysis is un-covered and its understanding demands for future in-depth studies.

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