Serum Level of Plasminogen Activator Inhibitor Type-1 in Addicted Patients with Coronary Artery Disease

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Original Article

Abstract

Background: Plasminogen activator inhibitor-1 (PAI-1) is a glycoprotein with inhibitory effects on the formation of plasmin from plasminogen by plasminogen activator. Thus, it prevents clot lysis in vessel walls. Several evidences prove the relationship between coronary artery disease and response to fibrinolytic therapy in patients with myocardial infarction with PAI-1 level. Opium addiction is one of the most important factors in causing myocardial infarction and cardiovascular events. This is due to it causing imbalance between coagulation and anticoagulation factors in the blood. This study was designed and implemented to determine the levels of PAI-I in opium-addicted patients with coronary artery disease in comparison with non addicts.

Methods: In this case-control study, 160 patients with coronary heart disease, which was confirmed by angiography results, were enrolled. All of the patients had a medical history, their creatine levels and lipid profile were evaluated, morphine urine test was performed, and after that a blood sample was taken to determine the levels of PAI-1. Thus, the 80 patients who had a positive morphine urine test result formed the case group, and the control group was constituted of the 80 patients with negative morphine test results. The two groups were matched.

Findings: Average level of PAI-1 in the control group was 2.4±2.6 and in the case group was 8.8 ± 9.1 and it was statistically significant ($P < 0.001$). The frequency of two vessel disease was higher in opium addicted patients than non-addicted patients and this was statistically significant ($P = 0.030$). However, the frequency of single vessel and three vessel disease was the same in the two groups. The two groups had no differences in age, lipid profile, and creatinine level. Moreover, females are at a higher risk of high PAI-1 levels.

Conclusion: PAI-1 levels in opium addicted patients with coronary heart disease are higher than other patients. In these patients, the risk of atherosclerosis and myocardial infarction is higher than normal.

Keywords: Opium addiction, Coronary heart disease, Plasminogen activator inhibitor-I (PAI-1)

Citation: Forood A, Malekpour-Afshar R, Mahdavi A. **Serum Level of Plasminogen Activator Inhibitor Type-1 in Addicted Patients with Coronary Artery Disease.** Addict Health 2014; 6(3-4): 119-26.

Received: 13.04.2014 **Accepted:** 21.06.2014

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Introduction

Plasminogen is an important factor in the internal fibrinolysis system and it is mainly synthesized in the liver and exists as inactivated form in plasma. It converts to its active form by plasminogen activator and causes decomposition of clots. In other words, it prevents the formation of intravascular thrombus. One way of inhibiting physiological fibrinolysis system is applied by plasminogen activator inhibitor-1 (PAI-1). In normal conditions balance exists between tissue plasminogen activators and plasminogen activator inhibitor-I.[1,2]

PAI-1 is a type of glycoprotein, and its gene is located on chromosome 7.[3] Moreover, its production is exacerbated by endothelial cells, hepatocytes, and fibroblasts in conditions such as local homeostasis and in the presence of endotoxin and cytokines.[3] This glycoprotein, with its inhibitory effect on plasminogen activator, prevents the formation of plasmin. In the early morning, PAI-1 levels naturally rise, but plasminogen activator levels do not change. It seems that during early morning, the activity of the fibrinolysis system reduces and intravascular thrombus formation tends to be high. Perhaps this is one of the main causes of heart attack during early mornings.[4]

Several studies have shown the relationship between levels of plasminogen activator inhibitor-1, and either stable or unstable coronary artery disease.[5,6] However, in patients with myocardial infarction, there is a clear association between PAI-1 levels and patient response to treatment with fibrinolytic agents; this has been demonstrated in several studies.[7] PAI-1 level is influenced by several factors such as patients' age, renal insufficiency, systolic blood pressure, insulin resistance, obesity, and triglyceride levels; however, it is not associated with cholesterol levels and smoking.[8]

There is increasing evidence indicating the importance of the internal fibrinolysis system and particularly PAI-1 level in the progression of atherosclerosis and that inhibiting glycoproteins can inhibit the development of atherosclerosis or even treat it. Thus, there are wide ongoing activities for the invention of compounds that inhibit the function of PAI-1. Although there is still no available combination that is approved for clinical use in humans, promising progress has been made in this field.[9] In recent years, opium addiction has been taken into account as a risk factor for coronary artery disease, myocardial infarction, and complications after coronary artery bypass surgery (graft occlusion).[10,11] Based on the evidence, this effect may be caused by increased inflammatory mediators by opium and disruption of the balance between coagulation and anticoagulation factors.[12]

Despite evidence regarding the role of opium in the advancement of atherosclerosis, so far, no study has been performed on its effects on plasma PAI-1 levels. In addition, based on clinical experiences, addicted patients with myocardial infarction showed weaker response to treatment with thrombolytic drugs. The risk of stent stenosis and myocardial infarction was higher in addicts than non-addicts, which could be due to the adverse impact of opium on the fibrinolysis system. In addition, due to the prevalence of opium addiction among patients in Iran, it is necessary to know the role of opium addiction and the appropriate respond for the prevention and treatment of these patients. Therefore, this study examined the effects of opium addiction on serum levels of PAI-1 in patients with coronary artery disease. Thus, the specialists in the field of health and macro-health system planners are provided with the required knowledge to plan and treat these patients according to an appropriate clinical approach.

Methods

This was a case-control study, conducted on patients with coronary artery disease who were hospitalized at Shafa Hospital affiliated to Kerman University of Medical Sciences, Iran. Patients who were undergoing coronary angiography and had over 70% stenosis in at least one coronary artery, an age of less than 65 years, body mass index below 30, and had no history of diabetes, kidney failure, liver disease, and hypertriglyceridemia. Despite the confounding effect of hypertension on PAI-1 levels, due to limited sample size, the patients with hypertension were not excluded from the study and its impact on the statistical analysis was considered. The case group consisted of opium addicts who had inhaled, ingested, or used opium as skewered stones or in the form of molasses,

burnt, heroin, and etcetera, for at least three times a week for at least three consecutive years. Patients who were not addicts, proven by their history and urine morphine strip test, were enrolled as control group.

Before entering the study, the researcher gave the necessary explanations regarding the goals and methods of the study to the patients or those accompanying them, and they were allowed to ask questions about the study. They were also assured that all information will remain confidential and unwillingness to participate in the study will not affect the normal process of treatment. Written informed consents were eventually obtained from all patients.

The patients' demographic data, including age, gender, height, weight, blood pressure, biochemical findings, and the history and amount of opium consumption, were recorded by the investigator in the data collection form. Angiographic films were reviewed by two physicians specializing in cardiovascular disease. Moreover, having coronary artery disease (70% stenosis in at least one coronary artery) was checked and recorded in the data collection form for each patient. Then, venous blood samples were taken from each patient in the morning of angiography after 12 hours fasting, and were kept for PAI-1 measurement in a temperature below 20 °C. Finally, after collecting blood samples from all patients participating in the study, PAI-1 was measured by enzyme-linked immunosorbent assay (ELISA) kit (KHC3071 manufactured by Invitrogen®) and the data were entered into the data collection forms. All collected data were entered into SPSS for Windows (version 16, SPSS Inc., Chicago, IL, USA) for analysis and were analyzed by central frequency indicators and distribution, Student's t-test, and chi-square test. In order to remove the effects of confounding variables, single univariate and multivariate regressions were used.

Results

In the present study, 160 patients with coronary artery disease were included; 80 patients entered into the study group and 80 patients in the control group. Of these patients, 106 were males (66.3%) and 54 were females (33.8%). The overall mean age of the patients was 53.8 ± 6.2, and the youngest patient was 40 years old and the oldest was 65 years old. Demographic characteristics of the two groups, including age, gender, body mass index (BMI), fasting blood sugar, and blood fat index, are shown in table 1. In all the cases of the demographic characteristics, except male gender, in both groups the differences were not statistically significant (P > 0.050).

The mean dosage used in the addicts group was 6.7 ± 3.5. Regarding the method of consumption of opium, 16 (20%) used it orally, 40 (50%) by inhalation, and 24 (30%) as skewer stone. Regarding the duration of addiction to opium, 1 patient (1.3%) had an addiction for three years, 5 patients (6.3%) between three to five years, and 74 patients (92.5%) for more than five years. Results of the involvement of coronary heart disease (CHD) in patients of both groups are shown in table 2. The patients of the case group, compared to the control group, had higher levels of involvement, which was two-vessel disease and was statistically significant (P = 0.030).

Average PAI-1 in all patients was 5.6 ± 7.9 ng/ml. This amount in the two groups of addicts and non-addicts was 8.8 ± 9.1 and 2.4 ± 2.6, respectively, and this difference between the two groups of control and case was significant (P < 0.001).

Due to the lack of normal distribution of amount of PAI-1, logarithm of the concentration

Table 1. Demographic characteristics of the patients in both case and control groups

Variables	Addicts	Non-addicts	P
Age (year)	54.0 ± 6.4	53.6 ± 5.9	0.700
BMI (kg/m^2)	26 ± 2	26 ± 2	0.500
Gender [male (%)]	60	46	0.019
Triglycerides (mg/dl)	131 ± 24	138 ± 26	0.090
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.4	0.560
FBS (mg/dl)	102 ± 11	101 ± 12	0.470
History of high blood pressure (%)	28	30	0.700

BMI: Body mass index; FBS: Fasting blood sugar

Table 2. Frequency of involvement of coronary artery disease in two case and control groups

Variables	Case group	Control group
	n (%)	
One vessel disease	22 (27.5)	42 (52.5)
Two vessel disease	46 (57.5)	26 (32.5)
Three vessel disease	12 (15.0)	12 (15.0)

of PAI-1 was used to compare the levels of this enzyme in the two study groups. The mean level of PAI-1 in the addicts' group was 0.7 ± 0.49 and in the case group was 0.14 ± 0.46, and this difference was statistically significant (P < 0.001).

Using univariate linear regression model and logarithm of PAI-1 as the dependent variable, the impact of demographic and clinical variables on the level of PAI-1 were also examined. Based on these results there was a significant relationship between opium addiction and PAI-1 levels (P < 0.001, β = 0.56). The impact of these variables on the level of PAI-1, using this model, is shown in table 3.

With regard to the likely effect of confounding variables on the relationship between addiction and PAI-1 level, multivariate linear regression model was used to examine the effect of variables with a P value of less than 0.2 in the univariate method. In other words, the only variables that were entered into multivariate models were variables that had a P value less than 0.2 in the univariate model. The results of this model showed that opium addiction was still significantly increasing the levels of PAI-1 (P < 0.001, β = 0.522). In this model, there was a significant relationship between female gender and level of this inhibitor (P < 0.001). In other words, female gender was an independent risk factor for increased levels of PAI-1. Furthermore, between cigarette smoking and levels of this inhibitor, there was a significant boundary relationship (P = 0.058). This means that smoking was determined as an independent risk factor for increasing the level of PAI-1. The related data are shown in table 4.

Discussion

This study, which was conducted on opium addicted and non-addicted patients with coronary heart disease, showed that the serum levels of PAI-1 in patients with opium addiction was about four times that in non-addicted patients. PAI-1 serum levels were higher in addicted patients and had no relationship with the dosage used.

Today, the defects of fibrinolytic activity have been identified in the case of atherothrombotic vascular disease.[13,14] This flaw in the occurrence of

Table 3. The impact of demographic and clinical variables on PAI-1 index using univariate linear regression LOG (PAI-1)

Variables	B (Beta)	SE	P
Gender (female)	0.307	0.087	0.001
BMI (km/m^2)	-0.033	0.018	0.066
Triglyceride (mg/dl)	0.000	0.002	0.923
Cholesterol (mg/dl)	-0.003	0.002	0.075
Smoking (pack/year)	0.180	0.094	0.058
CAD intensity	0.048	0.053	0.365
Opium addict or non-addict	0.522	0.625	< 0.001

BMI: Body mass index; CAD: Coronary artery disease; SE: Standard error

Table 4. Multivariate linear regression

Variables	B (Beta)	SE	P
Gender (female)	0.307	0.087	0.001
BMI (km/m^2)	-0.033	0.018	0.066
Triglyceride (mg/dl)	0.000	0.002	0.923
Cholesterol (mg/dl)	-0.003	0.002	0.075
Smoking (pack/year)	0.180	0.094	0.058
CAD intensity	0.048	0.053	0.365
Opium addict or non-addict	0.522	0.625	< 0.001

BMI: body mass index; CAD: Coronary artery disease; SE: Standard error

diseases, such as myocardial infarction (MI) and stroke, has been proven. However, its relationship with atherosclerosis is not yet known.[15,16] In patients with cardiovascular disease, especially in patients with a history of MI or acute coronary syndrome (ACS), impaired fibrinolytic activity was observed at rest and after physical activity and this disorder was associated with increased levels of PAI-1 in blood.[17,18] In addition, PAI-1 activity in diabetic patients with MI is very high.[19] Moreover, PAI-1 activity and very-low-density lipoprotein (VLDL), and triglyceride levels, respectively, had a positive and negative relationship with insulin sensitivity.[20] High levels of PAI-1 is considered as a predictive factor in the incidence of MI.[21]

Previous studies have shown that plasma fibrinogen levels in men with opium addiction are higher than men with coronary heart disease.[12] Studies have also showed a positive relationship between serum levels of fibrinogen and the incidence of MI.[22,23] It has also been shown that fibrinogen levels have increased the possibility of vessel lumen involvement.[22] Based on the findings of this study, the frequency of two-coronary vessel occlusion was increased in patients with addiction compared to non-addict patients, which confirmed the results of previous studies.[24] It Seems that with increased levels of fibrinogen and PAI-1 in patients addicted to opium, the rate of cardiac and cerebral artery occlusion also increased.

Some people and even a few doctors believe that opium can be effective in the prevention and mitigation of cardiovascular diseases and diabetes. In this study, it was shown that lipid variables and creatinine levels in both control and case groups had no difference, which was consistent with the results obtained from the study by Asgary et al.[24] However, in another study it was shown that morphine prescription increased levels of total cholesterol and LDL.[25] Other studies also showed that PAI-1 levels were higher in diabetic patients than in other patients, and that morphine injection increased blood sugar levels, despite the public perception.[26] Therefore, it seems that opium addicted patients who have diabetes are at higher risk than other people. Presently, there has been no study to assess the level of PAI-1 in patients with opium addiction, and this study, for the first time, examined PAI-1 level among these patients.

Based on the findings of this study, female gender was a risk factor for increased PAI-1. Nevertheless, findings of the study by Sadeghian et al. showed that men with opium addiction were more at risk of heart disease than men with diabetes.[27] It seems that in patients addicted to opium, due to the constant lipid parameters in comparison to other individuals and because of the positive relationship of these parameters with PAI-1 levels, lipid levels were higher. The present study confirmed this result. Followed by the high levels of PAI-1 in patients with opium addiction, the incidence of coronary artery lumen occlusion and cerebrovascular and cardiovascular diseases were higher than in normal individuals, and the reason for this is not yet clear.[28]

Based on previous studies, regarding PAI-1 serum levels in patients who were obese, PAI-1 levels increased with increasing BMI.[29] In the findings of this study, there was no significant relationship between PAI-1 levels and BMI amount in the patients of control and case groups. It appears that due to the compatibility between case and control groups and having BMI of more than 26 among the patients, the PAI-1 levels increased with the same ratio. This theory was consistent with the study by Shimomura et al.[30]

Studies showed that among the blood lipids, including triglycerides and cholesterol, only increased cholesterol levels caused the increased expression of PAI-1 in patients.[31] In addition, other studies showed that increase in morphine consumption caused an increase in total cholesterol and LDL levels.[25] However, the findings of this study did not show a significant relationship between increased levels of cholesterol or triglyceride and increased expression of PAI-1. It appears that in patients with high cholesterol levels, increased expression of PAI-1 occurs to an extent, and high cholesterol alone cannot increase PAI-1 levels. The results of the study by Vaisanen et al. also showed that increased blood cholesterol as LDL, has only a small role in increasing plasminogen and PAI-1 of patients.[32]

Numerous studies on the role of smoking and increased levels of PAI-1 have shown that cigarette smoking increases the risk of heart attack. Smoking increases the risk of atherosclerosis and PAI-1, and causes myocardial infarction.[33] The findings of this study showed that smoking marginally increased PAI-1 levels resulting in a marginal increase, and it appears that although smoking increased PAI-1, it had a small role in increasing its amount in the

body, this was consistent with the findings of the study by Scarabin et al.[34]

The limitations of this study were the lack of similarity between the gender of the participants of both groups and the impossibility of excluding patients with high blood pressure. It is recommended that these facts be considered in similar studies in the future.

Conclusion

Based on the findings of the current study, it was shown that in patients with opium addiction and coronary heart disease PAI-1 serum level was higher than other patients, and the extent of vascular occlusion and the risk of myocardial infarction were higher than normal individuals.

Conflict of Interests

The Authors have no conflict of interest.

Acknowledgements

We would like to thank the Physiology Research Center and Cardiovascular Department of Kerman University of Medical Sciences.

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تعیین سطح سرمی مهار کننده «فعال کننده پلاسمینوژن نوع یک» در بیماران مبتلا به بیماری عروق کرونر معتاد به تریاک

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مقاله پژوهشی

چکیده

مقدمه: مهار کننده فعال کننده پلاسمینوژن نوع یک (Plasminogen activator inhibitor-1 یا PAI-1) نوعی گلیکوپروتئین است که با اثر مهاری بر فعال کننده پلاسمینوژن، از تشکیل پلاسمین جلوگیری کرده و در نتیجه مانع از لیز شدن لخته در عروق می‌گردد. شواهد متعددی ارتباط بیماری عروق کرونر و همچنین پاسخ به داروهای فیبرینولیتیک در بیماران مبتلا به سکته قلبی را با سطح مهار کننده فعال کننده پلاسمینوژن نوع ۱ به اثبات رسانده‌اند. اعتیاد به تریاک یکی از عوامل مهم در ایجاد سکته‌های قلبی و حوادث عروقی قلبی- مغزی است و این امر می‌تواند ناشی از نقش تریاک در بر هم زدن تعادل بین شاخص‌های انعقادی و ضد انعقادی باشد. این مطالعه با هدف تعیین سطح PAI-1 در بیماران معتاد به تریاک مبتلا به بیماری عروق کرونر طراحی و اجرا گردید.

روش‌ها: مطالعه حاضر به صورت مورد- شاهدی بر روی ۱۶۰ بیمار مبتلا به بیماری عروقی قلب که با آنژیوگرافی نتایج آن‌ها تأیید شده بود، صورت پذیرفت. پس از بررسی نمودن سطح شاخص‌های چربی و کراتینین و تست مورفین ادرار، از تمام بیماران یک نمونه خون جهت بررسی سطح سرمی PAI-1 گرفته شد. بیمارانی که نتیجه مورفین ادرار مثبت داشتند، وارد گروه مورد و بیماران با تست منفی مورفین ادرار وارد گروه شاهد و دو گروه با یکدیگر همسان‌سازی شدند.

یافته‌ها: میانگین سطح سرمی مهار کننده فعال کننده پلاسمینوژن نوع یک در گروه شاهد ۲/۶ ± ۲/۴ و در گروه مورد ۹/۱ ± ۸/۸ نانوگرم در میلی‌لیتر و از نظر آماری معنی‌دار بود (P < ۰/۰۰۱). همچنین بیماران معتاد به تریاک دارای انسداد عروقی با تعداد رگ بیشتر بودند که از نظر آماری معنی‌دار بود (P = ۰/۰۳۰). از نظر شاخص‌های چربی، کراتینین و سن بیماران تفاوت آماری معنی‌داری وجود نداشت، تنها در بیماران جنس زن سطح مهار کننده فعال کننده پلاسمینوژن نوع یک بیشتر بود.

نتیجه‌گیری: سطح سرمی PAI-1 در معتادان به تریاک دچار بیماری عروقی قلب نسبت به سایر بیماران بیشتر و به دنبال آن میزان انسداد عروقی و خطر بروز انفارکتوس قلبی نیز بیشتر از افراد عادی می‌باشد.

واژگان کلیدی: اعتیاد به تریاک، بیماری عروقی قلب، فعال کننده پلاسمینوژن نوع یک

ارجاع: فرود افسانه، ملک‌پور افشار رضا، مهدوی امین. **تعیین سطح سرمی مهار کننده «فعال کننده پلاسمینوژن نوع یک» در بیماران مبتلا به بیماری عروق کرونر معتاد به تریاک.** مجله اعتیاد و سلامت ۱۳۹۳؛ ۶ (۴-۳): ۱۲۶-۱۱۹.

تاریخ دریافت: ۹۳/۱/۲۴ **تاریخ پذیرش:** ۹۳/۳/۳۱

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