

# Comparison between Homocysteine, Fibrinogen, PT, PTT, INR and CRP in Male Smokers with/without Addiction to Opium

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## Original Article

### Abstract

**Background:** Regarding the limited studies about effects of addiction on coagulation factors as a risk factor for increasing coagulation, and its relation to coronary artery disease, we decided to investigate the effect of opium on inflammatory and coagulation factors in a controlled setting.

**Methods:** This case-control study was performed using two groups of smoking males addicted to opium (27 cases) and not addicted to opium (27 cases). After collecting demographic data, venous blood samples were gathered and sent to laboratory for measuring homocysteine, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR), and C-reactive protein (CRP) quantity. In order to analyze the data, we used independent t-test plus Mann-Whitney test with significance level of  $P < 0.05$ .

**Findings:** The average age in this study was  $32.2 \pm 6.2$  in case group and  $33.3 \pm 6.2$  in control group. Comparing case and control groups regarding age and education showed no significant difference ( $P = 0.598$  and  $P = 0.848$ , respectively). Mean daily smoking in case group was  $7.9 \pm 5.4$  and  $8.1 \pm 5.0$  in control group. Mean smoking duration in case group and control group was  $10.1 \pm 6.5$  and  $9.0 \pm 7.2$  years, respectively. There was no significant difference between two groups regarding smoking duration ( $P = 0.567$ ). Comparison of inflammatory and coagulation factors showed no significant difference except for CRP and fibrinogen for which  $P = 0.661$  and  $P = 0.889$ , respectively. Consumption-based comparison of inflammatory and coagulation factors showed no significant difference except for PT in oral and inhaled consumptions which showed a significant difference ( $P = 0.035$ ).

**Conclusion:** Results of this study suggest that opium addiction can be an influential factor in blood parameters and can lead to inflammatory and coagulation processes complications.

**Keywords:** Addiction; Homocysteine; Fibrinogen; Prothrombin time; Partial thromboplastin time; International normalized ratio; C-reactive protein

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## Introduction

Coronary artery disease is currently a common disease worldwide and 1.3 million people suffer myocardial infarction annually. Based on World Health Organization (WHO), death rate caused by coronary artery disease will increase from 7.2 million in 2002 to 11.2 million in 2020.<sup>1</sup> Chronic disease of coronary arteries is caused by an obstruction by atherosclerotic plaque. Risk factors of atherosclerosis in coronary arteries include: diabetes, hypertension, smoking, older ages, hyperlipidemia, increased fibrinogen and homocysteine, lipoprotein (a) and overweight.<sup>1</sup>

There are reports that suggest there is a significant relationship between increased homocysteine, fibrinogen, and C-reactive protein (CRP) and risk of coronary artery disease. Various researchers have studied the relationship between hyperhomocysteinemia and cardiovascular disorders such as arterial thrombosis and coronary artery diseases.<sup>2</sup> Moreover, hyperhomocysteinemia has been found to be a predictive factor for increased pulse pressure and arterial stiffness.<sup>3</sup>

On the other hand, in recent years, drug use has increased in many countries around the world and in Iran. Drug addiction is a huge medical problem today.<sup>4</sup> Iran is a developing country in facing changes in trends of drug use towards higher consumption. In a cross-sectional study in Iran during 2008, it was found out that 2 million people were drug users and the number has increased significantly regarding the annual rate of addiction (8.0%) and population increase rate (2.63%). Common people and even some physicians believe that opium has some beneficial effects on cardiovascular diseases.<sup>5</sup> This can motivate some people to use opium and therefore, increase addiction in the society. There is an urgent need for more studies regarding these problems.

Some studies found a moderator role for opium use in CVD risk factors while others found harmful effects.<sup>6,7</sup> Among studies of this kind is the study of Asgary et al.<sup>8</sup> which showed that opium use did not have any effect on reducing blood sugar, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and Malondialdehyde in patients with drug addiction compared to the control group.

Bazzano et al.<sup>9</sup> concluded that smoking can increase CRP, fibrinogen and homocysteine levels in body. Also Masoomi et al.<sup>10</sup> found that plasma fibrinogen level in addicted males with opium was significantly higher than non-addicted males. Based on the study by Ghazavi et al.,<sup>11</sup> CRP level in opium-addicted cases was significantly higher.

Regarding the limitations in studies about opium-addiction effect on coronary artery disease, and because of some beliefs about usefulness of opium, we decided to investigate the effect of opium in a controlled setting (without confounding factors) on inflammatory and coagulation factors, plus the effects of different ways of opioid consumption on the mentioned factors.

## Methods

This case-control study was performed using two groups of smoking males addicted to opium (27 cases) and not addicted to opium (27 cases). The reason males were chosen for this study was that addiction is more common among men and they are more accessible for the study.

Inclusion criteria were addiction to opium, smoking, male and age between 20 to 50 years.

Exclusion criteria were having diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease and other cardiovascular diseases, history of having thrombosis in first degree relatives, heavy smokers, uncooperative patient, and dissatisfaction with participation in the study. Sampling was performed using available method in central prison and addiction treatment center of Birjand, Iran, during 2014.

People with opium addiction were determined based on Diagnostic and Statistical Manual of Mental Disorders-4<sup>th</sup> Edition (DSM-IV) criteria and consumption of at least once a day for 12 months. Smoking habit was determined based on at least one cigarette daily for one year.

After recording demographic and medical history of every participant, fasting blood samples of 10 ml in 3 distinct test tubes were taken. One sample was centrifuged immediately and the serum was separated and measured regarding CRP and homocysteine using enzyme-linked immunosorbent assay (ELISA) method.

Prothrombin time (PT) and partial thromboplastin time (PTT) tests were done on the second sample using proper kits and International Normalized Ratio (INR) was calculated accordingly.

**Table 1.** C-reactive protein (CRP) and homocysteine, fibrinogen, partial thromboplastin time (PTT), International Normalized Ratio (INR), prothrombin time (PT) in both groups

Variable	Group	Mean ± SD	t-test	P
PT	Case	12.30 ± 0.60	t = -0.970, df = 52	0.337
	Control	12.45 ± 0.48		
INR	Case	0.90 ± 0.07	t = -0.886, df = 52	0.380
	Control	0.92 ± 0.06		
PTT	Case	31.30 ± 2.07	t = 0.518, df = 52	0.607
	Control	30.96 ± 2.62		
Fibrinogen	Case	337.00 ± 168.82	Mann-Whitney U = 145.50, Z = -3.66	< 0.001
	Control	183.81 ± 168.27		
Homocysteine	Case	18.42 ± 11.53	t = -0.845, df = 52	0.402
	Control	20.77 ± 8.68		
CRP	Case	6.18 ± 5.14	Mann-Whitney U = 223.50, Z = -2.44	0.015
	Control	2.89 ± 3.34		

SD: Standard deviation; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International Normalized Ratio; CRP: C-reactive protein; df: Degree of freedom

Fibrinogen test was performed for the third sample. Results of the tests were recorded in corresponding files. Data were analyzed using SPSS for Windows (version 15, SPSS Inc., Chicago, IL, USA)  $P < 0.05$  as the significance factor. Normal distribution of the data was investigated and for descriptive indices, t-test was used. Mann-Whitney U test was used when there was not a normal distribution in the data.

## Results

The average age in this study was  $32.2 \pm 6.2$  in case group and  $33.3 \pm 6.2$  in control group. Case and control groups showed no significant difference regarding age and education ( $P = 0.598$  and  $P = 0.848$ , respectively).

About 96.5 percent of participants were in business work. Regarding education, the participants were divided into five groups of illiterate, elementary education, pre-high school, high school and university education. Most of the participants had elementary education and there

was not any significant difference between case and control groups ( $P = 0.848$ ).

Mean ± standard deviation (SD) of daily smoking in case group was  $7.9 \pm 5.4$  and  $8.1 \pm 5.0$  cigarettes in control group. Mean ± SD of smoking duration in case group and control group was  $10.1 \pm 6.5$  and  $9.0 \pm 7.2$  years, respectively and there was no significant difference between the two groups regarding smoking duration ( $P = 0.567$ ). Comparison of inflammatory and coagulation factors showed no significant difference except for CRP and fibrinogen ( $P < 0.050$  for the CRP and fibrinogen). With regard to consumption-based comparison of inflammatory and coagulation factors, only PT in oral and inhaled consumptions showed significant difference ( $P = 0.035$ ). About 44.4% of the addicts used opium once daily.

PT, INR, PTT, fibrinogen, homocysteine, and CRP were compared in this study and the results are shown in table 1. Table 2 shows the variables based on drug administration routes.

**Table 2.** Partial thromboplastin time (PTT), International Normalized Ratio (INR), prothrombin time (PT), fibrinogen, homocysteine and C-reactive protein (CRP) according to the route of drug administration

Variable	Addiction	Mean ± SD	t-test	P
PT	Inhaled	12.47 ± 0.51	t = -2.23, df = 25	0.035
	Oral	11.96 ± 0.64		
INR	Inhaled	0.92 ± 0.07	t = -1.40, df = 25	0.173
	Oral	0.87 ± 0.08		
PTT	Inhaled	31.17 ± 2.00	t = 0.45, df = 25	0.655
	Oral	31.56 ± 2.29		
Fibrinogen	Inhaled	336.78 ± 167.13	Mann-Whitney U = 69.5, Z = -0.139	0.889
	Oral	337.50 ± 184.26		
Homocysteine	Inhaled	18.75 ± 10.61	t = -0.20, df = 25	0.839
	Oral	17.77 ± 13.87		
CRP	Inhaled	6.43 ± 5.24	Mann-Whitney U = 72.50, Z = -0.438	0.661
	Oral	5.68 ± 5.19		

SD: Standard deviation; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International Normalized Ratio; CRP: C-reactive protein; df: Degree of freedom

## Discussion

This study was performed in order to investigate the effect of quantitative homocysteine, fibrinogen, PT, PTT, INR, and CRP in smoking men with/without opium addiction in Birjand. There were 27 male smokers in the case group and 27 smokers without addiction in the control group. Based on the results, there was no significant difference among groups regarding age, education, number of cigarettes smoked daily, and duration of smoking ( $P > 0.050$ ). This suggests that the matching process was performed well.

There was no significant difference between INR, PTT, PT in both case and control groups ( $P > 0.050$ ), which is in line with findings of Moloudi et al. who showed that serum S and C protein levels plus PT and PTT in case and control groups had no significant difference.<sup>12</sup>

Mirzaeipour et al. investigated the effect of opium consumption on inflammatory and coagulation factors in golden hamster, and showed that there was no significant difference between PT, PTT and INR in hamsters with/without opium consumption.<sup>13</sup> These results are consistent with the results of this study. Also, Nemati et al. concluded that coagulation factors do not change with drug usage,<sup>14</sup> which is consistent with the present study.

There was no relationship between drug use and blood coagulation. Also, investigation of plasma fibrinogen level of the two groups of participants suggested that fibrinogen serum level was significantly higher in drug users compared to the control group. The same result was found in Moloudi et al.'s study.<sup>12</sup> Similarly, Masoomi et al.<sup>10</sup> found that plasma fibrinogen level in inhaled addicted group was higher than control group.

Increased plasma fibrinogen is a risk factor for atherosclerosis including coronary artery disease, brain stroke and peripheral arteries involvement.<sup>15,16</sup>

Various studies have suggested a relationship between plasma fibrinogen level and severity of coronary artery disease using angiography. Most of these studies consider obstruction of the vessel lumen as the main reason for this problem which suggests that high levels of plasma fibrinogen is a risk factor for thromboembolism.<sup>17,18</sup>

However, Mirzaeipour et al.<sup>13</sup> and Naderi

et al.<sup>19</sup> found no significant relationship between drug use and increased fibrinogen in case group. This inconsistency may be a result of the difference between sample sizes of the studies. Lower levels of fibrinogen in opium-addicted patients can be explained by their lower rate of physical activity. Many studies have proved that sports and physical activities can reduce plasma fibrinogen level in the human body.<sup>20,21</sup> That is why addicts have higher levels of plasma fibrinogen.

In this study, serum homocysteine level in smokers with/without addiction was investigated. Results showed that there was not any significant difference between groups which is consistent with the results obtained by Mirzaeipour et al.<sup>13</sup> and Hamzei et al.<sup>22</sup> Also Tomedi et al.<sup>23</sup> did not find any relationship between drug use and serum homocysteine.

We investigated the CRP level in both case and control groups and found that serum CRP was significantly higher in case group which is in line with the study by Mirzaeipour et al.<sup>13</sup> However, Zeitune et al.<sup>24</sup> concluded that drugs can have an anti-inflammatory effect on CRP level. van Loon et al.<sup>25</sup> also focused on the anti-inflammatory effect of drugs. Similarly, Perrot et al.<sup>26</sup> showed that lower doses of opium have anti-inflammatory effects. On the other hand, Glattard et al.<sup>27</sup> found that increased density of endogenous opiates may suggest that lower doses of opium can reduce inflammatory processes in patient with systematic infections.

Study of Chadzinska et al.<sup>28</sup> demonstrated that lower doses of opium may decrease inflammatory leukocytes by inhibiting their migration from bone marrow. Inhibitory effect of morphine on a number of cells and their chemical properties will be removed after naltrexone therapy and its interference with opium receivers.<sup>28</sup> Krajnik et al.<sup>29</sup> found that higher doses of opium can cause life-threatening immunosuppression. This could be explained by the difference between animal samples and human samples. Also, smoking was an inclusion criteria in the present study which can increase inflammation in human body.<sup>30</sup>

Also, in the present study, PT, INR, PTT, fibrinogen, homocysteine and CRP were studied based on the route of administration and there was no significant difference except for PT which was higher in inhaled group of addicts ( $P = 0.035$ ). This is consistent with results of Mirzaeipour et al.<sup>13</sup>

Results showed that drug administration routes may have an influence on the risk of bleeding in surgeries or trauma and it is expected that inhaled drug users experience higher rates of bleeding. We did not find any other study regarding oral and inhaled drug users and inflammatory-coagulation factors.

### Conclusion

The results of our study showed that drug use (such as opium) change the level of some blood parameters. Addiction can increase the serum level of fibrinogen and CRP which are proposed risk factors of cardiovascular diseases. Based on

the predictions and necessary preparations, these risk factors must be taken into consideration. It is also worth to mention that routes of drug administration was another factor studied in this research. It is recommended that future studies include greater number of participants.

### Conflict of Interests

The Authors have no conflict of interest.

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## مقایسه بین مقادیر هموسیستئین، فیبرینوژن، INR، PTT، PT و CRP در دو گروه افراد سیگاری با و بدون اعتیاد به اویوم

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### مقاله پژوهشی

### چکیده

**مقدمه:** با توجه به محدود بودن پژوهش‌های موجود صورت گرفته در زمینه تأثیرات اعتیاد بر روی فاکتورهای انعقادی و همچنین، اثر آن بر روی بیماری‌های عروق کرونر، مطالعه حاضر با هدف تأثیر اویوم بر روی فاکتورهای التهابی و انعقادی در شرایط کنترل شده انجام شد.

**روش‌ها:** این مطالعه مورد-شاهدی در دو گروه افراد سیگاری معتاد (۲۷ مورد) و غیر معتاد (۲۷ مورد) انجام گرفت. پس از کنترل فاکتورهای دموگرافیک، یافته‌های آزمایشگاهی شامل هموسیستئین، فیبرینوژن، (INR) International Normalized Ratio، (PT) Prothrombin time، (PTT) Partial thromboplastin time و (CRP) C-reactive protein اندازه‌گیری گردید. داده‌ها با استفاده از آزمون‌های Independent t و Mann-Whitney در سطح معنی‌داری کمتر از ۰/۰۵ مورد تجزیه و تحلیل قرار گرفت.

**یافته‌ها:** میانگین سنی گروه تجربی و شاهد به ترتیب  $32/2 \pm 6/2$  و  $33/3 \pm 6/2$  سال بود و تفاوت معنی‌داری بین دو گروه از نظر سن ( $P = 0/598$ ) و سطح تحصیلات ( $P = 0/848$ ) وجود نداشت. میانگین تعداد سیگار روزانه در سال در گروه تجربی و شاهد به ترتیب  $7/9 \pm 5/4$  و  $8/1 \pm 5/0$  بود که تفاوت معنی‌داری بین دو گروه مشاهده نشد ( $P = 0/567$ ). تفاوت معنی‌داری بین دو گروه در مقایسه فاکتورهای آزمایشگاهی به جز فیبرینوژن ( $P < 0/001$ ) و CRP ( $P = 0/015$ ) وجود نداشت. بر اساس روش مصرف نیز تنها در مقادیر آزمایشگاهی PT بین دو گروه تفاوت معنی‌داری مشاهده گردید ( $P = 0/035$ ).

**نتیجه‌گیری:** نتایج مطالعه حاضر پیشنهاد می‌دهد که اعتیاد اویوم می‌تواند عامل تأثیرگذاری بر روی برخی فاکتورهای مرتبط خونی باشد و منجر به بروز فرایندهای التهابی و اختلالات انعقادی شود.

**واژگان کلیدی:** اعتیاد، هموسیستئین، فیبرینوژن، زمان پروترومبین، زمان نسبی پروترومبین، CRP

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