Elevated Plasma Homocysteine Concentration in Opium-Addicted Individuals

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Abstract

Background: Although the triggering role of both opium use and elevated plasma homocysteine level for progressing atherosclerosis and, therefore, appearing coronary heart disease has been clearly determined, no study are available with respect to the relation between these to risk profiles. In the present study and for the first time, we hypothesized that the opium addiction can be potentially correlated with elevated homocysteine concentration.

Methods: 217 persons (103 opium-addicted and 114 non-addicted) were randomly selected from the Kerman Coronary Artery Disease Risk Study (KERCADRS), Iran, as a population-based, epidemiological prospective study. In all participants, an enzyme immunoassay kit was used to measure homocysteine in serum samples.

Findings: The serum level of homocysteine was significantly higher in the opium-addicted ones compared to non-addicted individuals (11.49 ± 7.45 vs. 8.02 ± 3.87 µmol/l) (P < 0.001). In this regard, 21.3% of the opium users and only 3.2% of the non-users had homocysteine concentration > 15 µmol/l (P < 0.001). On the other hand, individuals addicted to opiates exhibited significantly elevated odds of having homocysteine level higher than 15 [odds ratio (OR) = 8.244, 95% confidence interval (CI) = 3.117-21.806]. Multivariable linear regression model showed that the opium addiction could strongly predict elevated homocysteine level in the study individuals [beta = 3.524, standard error (SE) = 0.852] (P < 0.001).

Conclusion: Opium consumption can be strongly accompanied with the elevation of plasma homocysteine concentration, and thus opium addiction can exhibit elevated odds of having hyperhomocysteinemia.

Keywords: Opium addiction, Homocysteine, Cardiovascular disease

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Introduction

The majority of prospective studies could show that elevated plasma total homocysteine level was an important risk factor for developing coronary atherosclerosis and pathological changes in cerebrovascular and peripheral vascular systems.\(^1\)\(^-\)\(^5\) Recent investigations have produced some probable mechanisms responsible for the appearance of atherosclerotic lesions following elevation of this biomarker including vascular endothelial defects, increased uptake of modified low density lipoprotein, stimulating proliferation of smooth muscles, and antithrombotic abnormalities.\(^6\) High levels of homocysteine are believed to promote the formation of oxidation products such as homocysteine and homocysteine disulfides, as well as homocysteine thiolactone, which can damage endothelial cells by excessive sulfation of collagen.\(^7\)\(^-\)\(^9\)

Furthermore, it has been suggested that the defects in intracellular homocysteine metabolism frequently an inadequate intake of folate or vitamins B-6 or B-12 as cofactors or substrates for the enzymes involved in homocysteine metabolism can result in elevated plasma homocysteine concentrations.\(^10\)\(^,\)\(^11\) These metabolic defects are usually occurred following abnormalities in either genetic or nutritional backgrounds.\(^12\)

Besides, the life-threatening events associated with the use of opium or its purified agents have captured the attention of clinical researchers. It has been demonstrated that serum levels of some biochemical risk factors for coronary artery disease (CAD) such as lipoprotein (a) and C-reactive protein were significantly higher in opium-addicted patients and these factors were major determinants of risk factor for premature atherosclerosis.\(^13\) Furthermore, in some recent clinical studies, role of opium addiction on progressing coronary atherosclerosis and its related poor outcome has been identified.\(^14\)\(^-\)\(^16\)

Although the triggering role of both opium use and elevated plasma homocysteine level for progressing atherosclerosis and, therefore, appearing coronary heart disease has been clearly determined, no study are available with respect to the relation between these to risk profiles. In the present study and for the first time, we hypothesized that the opium addiction can be potentially correlated with elevated homocysteine concentration and thus can trigger its serum level elevation.

Methods

The Kerman Coronary Artery Disease Risk Study (KERCADRS), Iran, is a population-based, epidemiological study among 6000 individuals aged 15-75 years and residence in Kerman city addressing the information of six risk factors of coronary artery disease (CAD) including serum lipids, physical activity, alcohol and drugs addiction, mental disorders like stress and depression, hypertension, and diet regimen.\(^17\)

These individuals were given the study questionnaires by a general practitioner about their medical history including CAD risk factors: current smoking history (patients regularly smoke a tobacco product/products 1 or more times per day or have smoked in the 30 days prior to admission),\(^18\) hypercholesterolemia (total cholesterol \(\geq 5.0\) mmol/l, high-density lipoprotein cholesterol \(\geq 1.0\) mmol/l in men, or \(\geq 1.1\) mmol/l in women, and triglyceride (TG) \(\geq 2.0\) mmol/l),\(^19\) family history of CAD (first-degree relatives before the age of 55 in men and 65 years in women),\(^20\) hypertension [systolic blood pressure (BP) \(\geq 140\) mmHg and/or diastolic BP \(\geq 90\) mmHg and/or on antihypertensive treatment],\(^21\) and diabetes mellitus (DM) [symptoms of diabetes plus at least one of the following: plasma glucose concentration \(\geq 11.1\) mmol/l, fasting plasma glucose \(\geq 7.0\) mmol/l, and two-hour postprandial (2-HPP) \(\geq 11.1\) mmol/l].\(^22\)

With regard to recording opium addiction rate, the participants were asked to disclose whether they have ever used any type of drug and still continue. Opium addiction was defined on the basis of the diagnostic and statistical manual of mental disorders-4\(^{th}\) edition (DSM-IV) criteria for substance dependence as regularly consumption of inhalation or orally opium more than 3 times per week.\(^23\) Based on this definition, participants were classified into two groups: 1- current opium-addicted cases (\(n = 850\)) and 2- non-addicted cases.

In current study and out of the defined KERCADRS study population, 217 men aged 40-70 years were randomly selected and prospectively underwent measurement of homocysteine. Those with malignant disease, severe renal insufficiency,
cirrhosis, active liver disease attributable to viral infection, and/or other acute infectious or inflammatory disorders were all excluded. The study was approved by the research and Ethics Committees of the Kerman University of Medical Sciences and informed consent was obtained from all participants.

BP was measured in sitting position after at least 10 minutes at rest using a Standard Mercury Manometer (Richter, Germany). If abnormal, BP was measured once again at the end of the session (at least 30 minutes after the first measurement) in the same conditions.

For biochemical analysis, blood samples of 5 ml were drawn after 12 hours overnight fasting for measuring lipid profile, fasting blood sugar (FBS), and also homocysteine. Plasma glucose was measured using the glucose oxidase peroxidase method (KIMIA Kit, Code 890410, Iran). The level of serum lipid profile was also determined by standard enzymatic procedures (KIMIA Kit, Code 890201 for serum TG, and Code 890303 for total cholesterol, Iran). An enzyme immunoassay kit (Axis-Shield Diagnostics, UK) was used to measure homocysteine in serum samples. Elevated homocysteine level in men was considered > 15 µmol/l. 24

The sample size was estimated by the power analysis and sample size (PASS) for Windows software (PASS, NCSS 2000). Based on the data on Masoomi et al. study,1 the groups size of 90 achieved 90% power to detect at least 3.0% increase in homocysteine level in the opium-addicted group, with a significance level (alpha) of 0.05. Allowing for a 10% dropout rate, the study required at least 100 participants per arm 1.

Results

Table 1 compares baseline characteristics between the opium-addicted and non-addicted subjects. Regarding measured BP, both systolic and diastolic BPs were significantly lower in the addicted group, while other parameters were similar across the two groups. With respect to the association between serum homocysteine levels, the level of this biomarker was significantly higher in the opium-addicted ones compared to non-addicted individuals (11.49 ± 7.45 vs. 8.02 ± 3.87 µmol/l) (P < 0.001). In this regard, 21.3% of the opium users and only 3.2% of the non-users had homocysteine concentration > 15 µmol/l (P < 0.001). On the other hand, individuals addicted to opiates exhibited significantly elevated odds of having homocysteine level higher than 15 [odds ratio (OR) = 8.244, 95% confidence interval (CI) = 3.117-21.806].

**Table 1. Baseline characteristics and laboratory parameters in study population**

| Characteristics                  | Opium-addicted group (n = 103) | Non-addicted group (n = 114) | P     |
|----------------------------------|---------------------------------|------------------------------|-------|
| Age (year) (mean ± SD)           | 43.26 ± 4.53                    | 42.39 ± 4.87                 | 0.091 |
| History of hypertension [n (%)]  | 17 (16.5)                       | 21 (18.4)                    | 0.711 |
| History of diabetes [n (%)]      | 10 (6.0)                        | 12 (7.2)                     | 0.659 |
| Systolic BP (mmHg) (mean ± SD)   | 113.13 ± 14.68                  | 116.38 ± 15.41               | 0.047 |
| Diastolic BP (mmHg) (mean ± SD)  | 76.86 ± 10.00                   | 79.02 ± 9.75                 | 0.054 |
| FBS (mg/dl) (mean ± SD)          | 101.85 ± 31.16                  | 101.74 ± 38.06               | 0.977 |
| Serum total cholesterol (mg/dl)  | 192.56 ± 41.84                  | 199.41 ± 43.64               | 0.143 |
| Serum TG (mg/dl) (mean ± SD)     | 173.93 ± 129.06                 | 178.79 ± 122.55              | 0.724 |
| Serum homocysteine (mg/dl)       | 11.49 ± 7.45                    | 8.02 ± 3.87                  | < 0.001 |

SD: Standard deviation; FBS: Fasting blood sugar; BP: Blood pressure; TG: Triglyceride
Among different laboratory parameters including FBS, systolic and diastolic BPs, and lipid profiles, homocysteine level had a significant linear correlation only with FBS ($r = 0.173$, $P = 0.002$) (Figure 1). Multivariable linear regression model (Table 2) showed that opium addiction could strongly predict elevated homocysteine level in the study individuals [$\beta = 3.524$, standard error (SE) = 0.852] ($P < 0.001$).

### Table 2. Multivariable linear analysis for determining role of opium addiction for predicting elevation of plasma homocysteine level

| Item                        | Beta   | SE     | P     |
|-----------------------------|--------|--------|-------|
| Opium addiction             | -3.524 | 0.852  | < 0.001 |
| Age                         | -0.105 | 0.092  | 0.253 |
| History of hypertension     | -0.100 | 1.171  | 0.932 |
| History of diabetes         | 1.274  | 1.662  | 0.445 |
| Systolic BP (mmHg)          | 0.014  | 0.043  | 0.736 |
| Diastolic BP (mmHg)         | -0.036 | 0.062  | 0.565 |
| FBS (mg/dl)                 | 0.032  | 0.014  | 0.024 |
| Serum total cholesterol (mg/dl) | 0.015 | 0.010  | 0.145 |

FBS: Fasting blood sugar; BP: blood pressure; SE: Standard error

Discussion

In some recent studies particularly on diabetics, it has been clearly determined an association between the elevation of plasma homocysteine levels and higher prevalence of some diabetes complications such as peripheral arteriopathy and nephropathy. Furthermore, it has been suggested that the elevated homocysteine can be associated with high levels of fibrinogen, lipoprotein (a), microalbuminuria, and BP levels. In some others, the association between serum homocysteine level and traditional CAD risk factors was only observed for systolic hypertension and there was no significant relationship between homocysteine level and...
other coronary risk profiles such as DM, hyperlipidemia, and smoking habit. We could show this relationship only for elevated blood sugar that the positive correlation was observed between homocysteine concentration and FBS. Recent studies have demonstrated that under diabetic conditions, the catabolism of homocysteine was enhanced by transcriptional regulation of hepatic cystathionine beta-synthase and these changes were prevented by treatment with insulin.

In fact, plasma homocysteine levels are elevated in patients with diabetes, particularly in patients with type 2 diabetes as well as in individuals in prediabetes states who exhibit insulin resistance. The levels of homocysteine in such individuals are also influenced by their insulin concentrations, therapy with insulin, and medications such as metformin and glitazones that can either raise or lower homocysteine levels. Although we showed a relationship between FBS and homocysteine level, but this relationship was not detected between this marker and presence or absence of the history of DM. It seems that a considerable number of our population with diabetes had an irregular and uncontrolled blood sugar on the time of study. Therefore, it should be assessed this relationship in non-diabetic population or on all patients with diabetes with regular antidiabetic regimens.

Based on our knowledge, this study was the first study that assessed changes in homocysteine level in opium addiction patients. In a study by Kulkarni et al., the effect of heavy alcohol consumption on serum malondialdehyde, homocysteine status, and glutathione-S-transferase activities in alcoholics consuming illicit liquor from the lower socioeconomic background. They showed an increase in serum homocysteine level in heavy alcohol drinkers and indicated that increasing homocysteine activities might enhance the susceptibility to vascular diseases in heavy illicit drinkers with poor nutritional status; however, it seems that the pathophysiological effects of opium use on concentration and activation of homocysteine might be different of alcohol use. It has been demonstrated that opiate addicts present lower levels in folic acid than the control group, but no significant differences were observed for vitamin B-12. This can explain the changes in level and homocysteine metabolism in opium users. Moreover, deleterious effects of opium consumption on homocysteine metabolism might be explained by its effects on nutritional status. Opium use can cause poor appetite and apathy regarding diet and nutrition.

Opiate addicts and especially those with heavier consumption, develop anorexia which is determined by the poor consumption of food and drink leading to malnutrition. Morabia et al. have deduced that opiate addicts replace foods that are rich in fat and animal proteins with those that are rich in carbohydrates, especially sucrose and alcohol. It can result in an abnormality in homocysteine metabolism or its related enzymatic synthesis processes. Although the current evidence on this subject should be provided more and our obtained relationship between plasma homocysteine level and opium addiction especially with considering amount and root of consumption should be studied more.

**Conclusion**

The study indicated that opium consumption can be accompanied with the elevation of plasma homocysteine concentration.

**Conflict of Interests**

The Authors have no conflict of interest.

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مقاله پژوهشی
چکیده
مقدمه: با وجود نقش فراوانی استفاده از تریاک و افزایش سطح هوموسیستئین در جهت بهبود آتروسکروزور، بررسی بیماری‌های قلبی-عروقی در رابطه با مصرف تریاک به دستور مطالعه قرار گرفته است. مصرف مواد مخدر یکی از جدی‌ترین مشکلات عمومی بشر در تمام جوامع و تریاک یکی از منابع مصرفی در ایران می‌باشد. در مطالعه حاضر انتباه به تریاک به طور بالقوه در ارتباط با افزایش غلظت هوموسیستئین بررسی گردد.

روش ها: ۲۱۷ نفر از افراد شرکت کننده در طرح قلب سالم مرکز تحقیقات فیزیولوژی کرمان (۱۰۳ نفر معتاد به تریاک و ۱۱۴ نفر غیر معتاد) وارد مطالعه شدند. مقیاس هوموسیستئین در این افراد با استفاده از کیت‌های Elisa انتزاع گردید.

یافته‌ها: مقدار هوموسیستئین در افراد معتاد به تریاک (۷/۴±۵/۰ میکرومول بر لیتر) نسبت به گروه مداوم (۳/۲±۵/۲ میکرومول بر لیتر) به طور معنی‌داری بیشتر بود (P<0/01). به طوری که مقیاس هوموسیستئین ۲/۲ درصد از افراد معتاد به تریاک و ۳/۲ درصد از افراد غیر معتاد به تریاک بود. به طور میانگین دارای بیش از ۱۵ میکرومول بر لیتر بود (P<0/01). مقدار سطح واکنش در افراد معتاد به تریاک (P<0/01) با اساس نمونه‌گیری خیزه و با استفاده از نکاتی به طور میانگین بیش از ۱/۵ درصد (odds ratio) OR = 8/۲۴۴ SE = 7/۲*۴ [Standard error] = Beta ۷/۲*۴ = 3/۲*۴ = ۲/۱۴۳. به این ترتیب تأثیر قابل معنی‌داری هوموسیستئین در افزایش فشار خون و احتمال بروز بیماری‌های قلبی-عروقی باقی خواهد ماند.

نتیجه‌گیری: انتباه به تریاک به طور قوی با افزایش مقادیر هوموسیستئین ارتباط دارد و این رابطه معنادار می‌باشد. افزایش مقادیر هوموسیستئین و افزایش مقادیر فشار خون و احتمال بروز بیماری‌های قلبی-عروقی باقی خواهد ماند.

واژگان کلیدی: انتباه به تریاک، هوموسیستئین، بیماری‌های قلبی-عروقی

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