Increasing the Risk of Stroke by Opium Addiction

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Introduction: Stroke is among the leading causes of mortality and morbidity in the world. Besides the identified risk factor, Ischemic stroke evidence show drug use develops or exacerbates the atherosclerotic process. The current study aimed at comparing cerebrovascular ultrasounds' changes in addicted and nonaddicted people who developed ischemic stroke. *Methods:* In the current cross-sectional study, a total of 133 patients with ischemic stroke who were admitted to Vali-Asr hospital from June 2016 to April 2017 were enrolled. For obtaining the quantitative data, *t* test or Mann-Whitney test was employed to compare the addict or no-addict groups, as well as, categorical data testing was performed using chi-square test. Also, the multiple logistic regression was used for identifying the factors and the significance level was set at 5%. *Results:* The current study was performed on 133 patients, among them 41 patients (30.8%) were opium addicted, and 92 patients (69.2%) were nonaddict. The mean [IQR] number of atherosclerotic plaques were significantly higher in opium addicted group in comparison with the nonaddicted group (3.0 [1.0-4.0] versus 1.5 [0.0-3.0], $P = .008$). The possibility of increasing the number of plaques in addicted patients was 1.42 times higher than the nonaddicted patients (odds ratio (95% confidence interval): 1.42 (1.11-1.81), $P = .005$). *Conclusion:* The findings demonstrated a significant difference in the vessel stenosis pattern between the addict and nonaddict ischemic stroke groups. To investigate the possible effects of opium use and its associated parameters, ie, dosage, duration of use, and the way of opium use on ischemic stroke, further studies are required.
Key Words: Stroke—opium—addiction—cerebrovascular accident

Introduction

Cerebrovascular accidents are known as the second cause of death, especially in the elderly population.[1] They have been divided into thrombotic and hemorrhagic categories. Focal cerebral ischemia is responsible for the occurrence of 80% of strokes which is due to cerebral occlusion, and the remaining 20% is due to hemorrhages.[2] Many risk factors of cerebrovascular diseases are the same as those for cardiovascular diseases, including pre-existing heart diseases (coronary artery disease [CAD], atrial fibrillation), hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, and age above 65 years.[3]

Based on the recent studies, opium addiction is proposed as a risk factor for CAD.[4] Some studies suggest that there is a relation between opium addiction and increased risk of ischemic stroke.[5,6] However, due to lack of sufficient data we cannot confirm such a hypothesis, and the existing data has some contradiction. Hamzei-Moghaddam et al reported that the frequency of opium consumption among ischemic stroke patients was higher than the healthy population, however, the order of carotid stenosis in addicted patients was similar to nonaddicts.[6] Rezvani et al found that oral use of opium has a preventive effect on the rise of ischemic stroke. They also added that the methods of opium use can have a role in the development of ischemic stroke where the inhalation method has no protective effect.[7]

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Due to cultural beliefs about the preventive effect of opium, prevalence of its addiction in developing countries such as Iran is higher than the developed countries.[8] Thus, it has been raised as a significant public health issue in the Middle East. According to the shortage of sufficient data about the correlation between opium addiction and ischemic stroke and carotid vessel stenosis, we aimed at evaluating the hypothesis that opium use can increase the prevalence of ischemic stroke and carotid vessel thrombosis and stenosis.

Materials and Methods

This case-control study was conducted under a protocol which was approved by the Human Research Committee of the Birjand University of Medical Science (under Number: ir. bums.REC.1395.117) and involved 133 patients who had experienced sudden focal neurological deficits of possible arterial origin with a duration of more than or equal to 24 hours. The patients were referred to Vali-Asr Hospital of Birjand, East of Iran, in June 2016 to April 2017. At the time of admission, brain computed tomography scan or magnetic resonance imagine was taken from all patients and analyzed by a neurologist for approving the non-hemorrhagic stroke. In order to exclude the embolic cause of stroke, trans thoracic Echocardiography and ECG were carried out for all patients. Patients who had a normal ventricular and valvular function and did not have any evidence of patent foramen ovale (PFO) or atrial septal defect in Echocardiography and without any evidence of Atrial Fibrillation in ECG, considered as non-embolic stroke. Using the L5-13 transducer with a linear configuration, a radiologist conducted the Carotid Doppler Ultrasonography for all patients, which was a Medison Accuvix V10 ultrasound system and had a custom-built sequence of imaging. Carotid stenosis, regardless of its severity, was compared between addicted and nonaddicted patients. The studied risk factors involved: dyslipidemia (treated or greater than or equal to 200 mg/dL), arterial hypertension (blood pressure over 130/80 mm Hg),[9] coronary heart disease (history of myocardial infarction, congestive heart failure, or angina), diabetes (treated or FBS greater than or equal to 126 mg/dL in 2 or more distinct measurements), opium dependence (more than a year of consumption according to DSM-IV criteria [Diagnostic and Statistical Manual of Mental Disorders]), and smoking (more than 5 daily cigarettes).

Data were analyzed by SPSS-19 software. The quantitative variables were set ahead by mean (standard deviation) or median (interquartile range), and the qualitative variables were shown by numbers (ratios). The normality was evaluated using the Kolmogorov-Smirnov test. The addicted and nonaddicted patients were compared using *t* test or Mann-Whitney test for quantitative data, as well as, Fisher's exact test or Chi-square test for categorical data. Also, the multiple logistic regression was used for identifying the factors and the significance level was set at 5%.

Results

A total of 133 patients were enrolled with age more than 50 years old, among them, 41 (30.8%) were addicted,

Table 1. *Comparison of demographic and clinical characteristics in addicts and nonaddicts*

Variable	Addict	Nonaddict	Test results
Age (year)	71.83 ± 12.73	71.39 ± 12.05	t = .19, *P* = .85
Gender			
Male	22 (53.7%)	48 (52.2%)	X^2 = .02, *P* = .51
Female	19 (46.3%)	44 (47.8%)	
Diabetes mellitus	9 (28.15)	23 (71.9%)	X^2 = .1, *P* = .47
Hypertension	22 (30%)	50 (70%)	X^2 = .08, *P* = .55
Dyslipidemia	10 (32.3%)	21 (67.7%)	X^2 = .12, *P* = .42
Cigarette smoking	10 (71%)	4 (29%)	X^2 = 2.21, *P* = .02
WBC (10^3/μL)	8.71 ± 2.63	7.43 ± 1.84	t = 2.48, *P* = .01
RBC (10^6/μL)	4.95 ± 1.11	4.80 ± .75	t = .72, *P* = .47
HGB (g/dL)	13.92 ± 2.20	13.48 ± 1.89	t = .91, *P* = .37
HCT (%)	41.69 ± 8.06	39.24 ± 7.27	t = 1.34, *P* = .18
MCV (fL)	84.61 ± 5.75	84.44 ± 5.91	t = .12, *P* = .91
PLT (10^3/μL)	233.64 ± 62.25	228.13 ± 63.00	t = .36, *P* = .72
FBS (mg/dl)	115.05 ± 40.58	115.04 ± 38.65	t = .01, *P* = .99
TG (mg/dL)	102.25 ± 45.11	125.63 ± 41.78	t = 1.72, *P* = .09
TC (mg/dL)	155.58 ± 40.49	171.59 ± 39.30	t = 1.62, *P* = .11
HDL (mg/dL)	37.71 ± 11.35	37.58 ± 10.35	t = .05, *P* = .96
LDL (mg/dL)	126.08 ± 52.06	118.14 ± 38.92	t = .24, *P* = .81

FBS, fasting blood sugar; HCT, hematocrit; HDL, high-density lipoproteins; Hgb, hemoglobin; LDL, low-density lipoproteins; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PLT, platelet; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

Table 2. *Number of plaques and stenosis percentage of the addicted and nonaddicted patients*

Variable	Addict median [IQR]	Nonaddict median [IQR]	Result test
Number of plaque	3.0 [1.0-4.0]	1.5 [0.0-3.0]	Z = 2.64, *P* = .008
Vascular stenosis in the right side	30.0 [18.0-44.0]	28.0 [10.0-43.0]	Z = .71, *P* = .47
Vascular stenosis in the left side	32.0 [15.0-49.0]	27.0 [8.0-44.0]	Z = 1.31, *P* = .19
Calcified plaques	2.0 [1.0-3.0]	1.0 [1.0-2.0]	Z = 1.39, *P* = .16
Hypoecho	1.0 [0.0-2.0]	.5 [0.0-2.0]	Z = .79, *P* = .43
Internal media thickness	1.0 [.9-1.1]	.89 [.8-1.0]	Z = 3.37, *P* = .001

and 92 (69.2%) were nonaddicted. The mean age of addicted and nonaddicted patients were equal to 71.83 ± 12.73 and 71.39 ± 12.05 years, respectively. In the addicted patients, 22 (53.7%) were male and 19 (46.3%) were female, and in the nonaddicted patients, 48 (52.2%) were male and 44 (47.8%) were female. Among the risk factors of stroke, the frequency of smoking was significantly higher in addicted than nonaddicted patients. White blood cell count was significantly different between addicts and nonaddicts. Laboratory data and clinical characteristics of patients are shown in Table 1.

The mean [IQR] of plaques of addicted and nonaddicted patients were respectively equal to 3.0 [1.0-4.0] and 1.5 [0.0-3.0] with a significant difference in the number of plaques between them (Z = 2.64, *P* = .008). The percentage of vascular stenosis of carotid in the right and left sides in addicted patients was higher than non addicted patients, although the differences were not significant. Also, IMT in the addicted patient was significantly higher than nonaddicted (Table 2).

By adjusting the effect of cigarette smoking, variables that were significant (<.2 in the Mann-Whitney test) were evaluated in the multiple logistic regression model. Four variables including the number of plaques, vascular stenosis in the left side, the number of calcified plaques, and internal media thickness were analyzed using the logistic regression model (Table 3), and they showed that the number of plaques and IMT were significant. The possibility of increasing the number of plaques in the addicted patients was 1.42 times higher than the nonaddicted patients (odds ratio (95% confidence interval): 1.42 (1.11-1.81), *P* = .005). The Hosmer-Lemeshow goodness-of-fit test was found to be insignificant ($X^2 = 5.24$, df = 8, *P* = .73). Thus, the null hypothesis stated that the model fitting the data could not be rejected.

The results of Pearson correlation showed that there was no significant relationship between the duration of drug use and the number of plaque (*P* = .17), vascular stenosis in the right (*P* = .23) and left (*P* = .26) sides, calcified plaque (*P* = .19), hypoecho (*P* = .46), and internal media thickness (*P* = .15) (Table 4).

Discussion

The prevalence of opioid compounds is increasing in societies and getting aboard even in young ages. Based on previous studies, the emergence of opioid compounds in Iran amounts to 26.5% among people aged 19-76 years, and as involved in the 13-24 years old group, the rates are .8 % for opium, 1% for heroin, and .3% for morphine.[10,11]

Opioid addiction is accompanied by an increased risk of death with different causes.[12-16] According to the systematic review conducted by Degenhardt et al, due to AIDS-related disease, opioid addiction increases crude mortality rates by 1.8, overdose-related disease .65, trauma-related disease .25, liver-related disease .16, cancer-related disease .06, and cerebrovascular disease .001 deaths per 100 people.[17] Various studies were conducted to evaluate the relationship between opium addiction and the emergence of arterial diseases such as CAD and stroke showed contradictory results. Najafipour et al in a study on 5900 subjects with coronary or cerebral arterial disease reported that opium addiction did not increase the risks of hypertension, diabetes, and lipid profile, which were significant risk factors for the incidence of CAD and stroke.[18] Regarding hypertension, dyslipidemia, and diabetes mellitus, our study also showed no significant difference between stroke patients with and without addiction. However, there was a considerable difference in cigarette smoking between the 2 groups, such that 71% of the patients with opium addiction were smokers in contrast to the 29% smoking rate of the nonaddicted patients.

According to our results, opium addiction could be considered as a risk factor for stroke. Moqaddam et al's study which was in agreement with our results reported that opium dependency could be regarded as an independent

Table 3. *Estimated number of plaques and stenosis percentage in addicts and nonaddicts using multiple logistic regression*

Variable	B(SE)	OR (95%CI)	*P* value
Number of plaques	.35 (.12)	1.42 (1.11-1.81)	.005
Vascular stenosis in the left side	.007 (.01)	1.01 (.98-1.03)	.54
Calcified plaques	.32 (.18)	1.37 (.95-1.97)	.09
Internal media thickness	.91 (.35)	2.48 (2.27-10.94)	.01

Table 4. *Correlation between duration of drug use and number of plaques and stenosis percentage*

Variable	Duration of drug use
Number of plaque	r = .23, *P* = .17
Vascular stenosis in the right side	r = .21, *P* = .23
Vascular stenosis in the left side	r = .19, *P* = .26
Calcified plaques	r = .22, *P* = .19
Hypoecho	r = .13, *P* = .46
Internal media thickness	r = .25, *P* = .15

risk factor for stroke. Plasma fibrinogen and coagulability increment were the reason for the adverse effects of opium on vascular stenosis in this study.[19] Also, Rezvani et al reported that oral opium addiction was a protective factor for ischemic stroke (odds ratio .211, confidence interval 95% .079-.564, *P* = .002) but not CAD, and inhaled addiction had a significant effect on the occurrence of these vascular complications. This study focused on the effect of opium addiction on the incidence of stroke. Another study concluded that the method of using opium and its amount were not associated with ischemic stroke.[20] In a case-control study of 98 subjects who had opioid in their blood sample with 97 subjects with negative blood samples, Marmor et al reported that long-term opioid exposure was associated with decreased severity of CAD and could have a protective effect.[21]

The primary pathology of atherosclerosis was indicated by endothelial injury and disposal of proteoglycans. There will be a following accumulation of Low-Density Lipids in the intima that is then oxidized and becomes cytotoxic, proinflammatory, chemotaxis, and proatherogenic. These proinflammatory cytokines induced macrophage derivation from monocytes and participated in the inflammatory response that expanded to the subendothelial layer. Lipids subsequently improved the derived macrophages. Finally, the accumulation of these apoptotic cells and cholesterol crystals led to the formation of atherosclerotic plaques. Experimental studies showed that oxidized Low-Density Lipids and monocyte chemotactic protein-1 (MCP-1) were the major atherosclerogenic chemokines and receptor of MCP-1(monocyte/macrophages (CCR2)) which were upregulated during plaque formation.[22-24]

Recent studies showed that opioid derivations had an immunomodulatory effect.[25,26] In an experimental study, Othman evaluated the relation between morphine administration, MCP-1 level, and apoptosis frequency, and found that the concentration of MCP-1 and apoptosis following morphine administration has been raised in a dose-dependent manner.[27] Based on these studies, opioids could lead to atherosclerotic plaques in vessels. There was only 1 study for evaluating the relationship between opium addiction and carotid atherosclerotic plaques in humans, and it reported no significant correlation between opium and carotid plaques,[6] a result which was in disagreement with ours. Another study showed that the amount of carotid stenosis in patients who were candidates for CABG was not significantly different between the 2 addicted and nonaddicted groups.[28] Our study revealed that opium addiction was significantly associated with the formation of internal carotid artery plaques, a finding that was in disagreement with other findings.

We have found an insignificant increase in the left side carotid stenosis in addicted patients. On the contrary, right side carotid stenosis overrode in nonaddicted patients. Moreover, the number of calcified plaques was higher in addicted patients. Also, internal media thickness was significantly higher in opium addicted patients. Hamzei-Moghaddam et al found that the differences of vascular stenosis frequency in left and right sides of carotid between the addicted and nonaddicted patients were not statistically significant. They also found that regarding stenosis, there were no statistically significant differences between the left and right arteries.[6] Another study showed that opium addiction had no significant relationship with maximum intima-media thickness and had no worse effects on the progression of atherosclerosis.[29] There were limited studies based on vessels ultrasound findings, and thus we could not compare our results with other studies; so, further studies were needed to evaluate the difference in carotid stenosis between addicted and nonaddicted patients. Use of opium may have a detrimental effect on different risk factors of atherosclerotic plaques formation, including apolipoprotein A, apoli-poprotein B,[30] C-reactive protein, factor VII, fibrinogen,[30-32] lipoprotein (a), Homocysteine,[33] Plasminogen Activator Inhibitor-1,[34] decreased Plasma Adiponectin,[35] increased oxidative stress,[8] and elevation of serum prolactin level. Therefore, the increased risk of myocardial infarction or ischemic stroke can be explained by the aforementioned outcomes of addiction.

Likewise, inflammation is an essential component in the pathophysiology of atherosclerosis. According to evidence, opium addicts have higher levels of inflammatory mediators, ie, CRP, IL-17, and IL-1 receptor antagonist.[36] Hence, the accelerated atheroma formation in opium addicts can be attributed to their enhanced inflammatory state.[8] Besides, using opium may have unfavorable effects on lipid metabolism,[8,37] and results in physical inactivity, obesity, and depression.

Limitations

Although we did our best to conduct a well-designed research, our study suffered from certain limitations. Given the cross-sectional design of this study, hence, we could not deduce causality for any of these correlations since unknown factors may explain the observed. Some key elements in patients' lifestyle (eg, diet and socioeconomic status) were not considered in this study. Also, in this study, inhalation method for opium use did not involve large numbers of individuals. The number of participants included in this subgroup to establish a relationship between the method of using and carotid stenosis was nearly low. More extensive data sets and enhanced data collection methods are needed in future studies to improve the accuracy of results.

Conclusion

Finally, this study showed that the frequency of carotid atherosclerotic plaques in opium addicted patients was higher than nonaddicted patients and undergoing stroke and opium addiction was associated with plaque formation in the internal carotid artery. Contrary to the popular opinion, opium addiction could be considered as a risk factor for stroke, so prevention of opium addiction could decrease the frequency of stroke.

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References

1. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 study. Neuroepidemiology 2015;45:161-176.
2. Díaz-Guzmán J, Egido J, Gabriel-Sánchez R, et al. Stroke and transient ischemic attack incidence rate in Spain: the IBERICTUS study. Cerebrovasc Dis 2012; 34:272-281.
3. Leira Y, Seoane J, Blanco M, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. Springer; 2017.
4. Sadeghian S, Darvish S, Davoodi G, et al. The association of opium with coronary artery disease. Eur J Cardiovasc Prev Rehab 2007;14:715-717.
5. Moqaddam AH, Musavi SMRA, Khademizadeh K. Relationship of opium dependency and stroke. Addict Health 2009;1:6.
6. Hamzei-Moghaddam A, Shafa MA, Khanjani N, et al. Frequency of opium addiction in patients with ischemic stroke and comparing their cerebrovascular doppler ultrasound changes to non-addicts. Addict Health 2013;5:95.
7. Rezvani MR, Ghandehari K. Is opium addiction a risk factor for ischemic heart disease and ischemic stroke? J Res Med Sci 2012;17:958.
8. Masoudkabir F, Sarrafzadegan N, Eisenberg MJ. Effects of opium consumption on cardiometabolic diseases. Nat Rev Cardiol 2013;10:733.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension 2018;71:1269-1324.
10. Shakibi MR. Prevalence of opium addiction in Iranian drivers 2001-2003. J Med Sci 2004;4:210-213.
11. Ahmadi J, Hasani M. Prevalence of substance use among Iranian high school students. Addict Behav 2003;28: 375-379.
12. Ghaderi A, NasehGhafoori P, Rasouli-Azad M, et al. Examining of thallium in cigarette smokers. Biol Trace Elem Res 2017: 1-7.
13. Alinejad S, Zamani N, Abdollahi M, et al. A narrative review of acute adult poisoning in Iran. Iran J Med Sci 2017;41(2):327-346.
14. Alinejad S, Ghaemi K, Abdollahi M, et al. Nephrotoxicity of methadone: a systematic review. SpringerPlus 2016;5:2087.
15. Mehrpour O, Sheikhazadi A, Barzegar A, et al. Comparison of quantitative and qualitative dermatoglyphic characteristics of opium addicts with healthy individuals. Addict Health 2016;8:76.
16. Alinejad S, Kazemi T, Zamani N, et al. A systematic review of the cardiotoxicity of methadone. EXCLI J 2015;14:577.
17. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta analysis of cohort studies. Addiction 2011;106:32-51.
18. Najafipour H, Masoomi M, Shahesmaeili A, et al. Effects of opium consumption on coronary artery disease risk factors and oral health: Results of Kerman Coronary Artery Disease Risk factors Study a population-based survey on 5900 subjects aged 15-75 years. Int J Prev Med 2015;6:42.
19. Moqaddam AH, Musavi SM, Khademizadeh K. Relationship of opium dependency and stroke. Addict Health 2009;1:6-10.
20. Ghayeghran A, Janeshin S, Saberi A, et al. The relationship between opium addiction and ischemic stroke. J Guilan Univ Med Sci 2016;24:42-49.
21. Marmor M, Penn A, Widmer K, et al. Coronary artery disease and opioid use. Am J Cardiol 2004;93:1295-1297.
22. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006;47:C7-C12.
23. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 2011;17:1410-1422.
24. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;145:341-355.
25. Martin JL, Koodie L, Krishnan AG, et al. Chronic morphine administration delays wound healing by inhibiting immune cell recruitment to the wound site. Am J Pathol 2010;176:786-799.
26. Hatsukari I, Hitosugi N, Dinda A, et al. Morphine modulates monocyte−macrophage conversion phase. Cell Immunol 2006;239:41-48.
27. Othman GQ. Induction of liver oxidative damage and monocyte chemoattractant protein-1 in opium addicted male rats. Polytechnic 2015;5(1):38-50.
28. Shirani S, Shakiba M, Soleymanzadeh M, et al. Can opium abuse be a risk factor for carotid stenosis in patients who are candidates for coronary artery bypass grafting. Cardiol J 2010;17:254-258.
29. Saadatnia M, Ebrahimi H, Tajmirriahi M. The effect of opium/INS; addiction on carotid intima media thickness. J Neurol Sci 2013: e217.
30. Asgary S, Sarrafzadegan N, Naderi GA, et al. Effect of opium addiction on new and traditional cardiovascular risk factors: do duration of addiction and route of administration matter? Lipids Health Dis 2008;7:42.

31. Naderi G, Asgary S, Sadeghi M, et al. Comparing plasma level of CRP, factor VII, fibrinogen; platelet counts, systolic and diastolic blood pressure in smokers with opium addicted smokers. J Qazvin Univ Med Sci 2005;9:3-7.
32. Moloudi A, Sabzi F, Shahhosaini E. Analysis of coagulation tests, proteins C and S, and plasma fibrinogen in addicts and non-addicts with coronary artery disease. J Kermanshah Univ Med Sci 2014;17:812-814.
33. Masoomi M, Azdaki N, Shahouzehi B. Elevated plasma homocysteine concentration in opium-addicted individuals. Addict Health 2015;7:149.
34. 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;6:119.
35. Shahouzehi B, Shokoohi M, Najafipour H. The effect of opium addiction on serum adiponectin and leptin levels in male subjects: a case control study from kerman coronary artery disease risk factors study (KERCADRS). EXCLI J 2013;12:916.
36. Saadat H, Ziai SA, Ghanemnia M, et al. Opium addiction increases interleukin 1 receptor antagonist (IL-1Ra) in the coronary artery disease patients. Plos One 2012;7:e44939.
37. Najafipour H, Beik A. The impact of opium consumption on blood glucose, serum lipids and blood pressure, and related mechanisms. Front Physiol 2016;7:436.