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Original Article

Investigating the Relationship between Carotid Intima-Media Thickness (CIMT), Opium Addiction, and Components of the Metabolic Syndrome

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Abstract
Background: Atherosclerosis has an essential role in causing cardiovascular diseases. Various factors affect the risk of coronary artery atherosclerosis, and the increase in the carotid intima-media thickness (CIMT) is a primary marker for detecting atherosclerotic changes in the artery wall. Since opioid use is one of the leading social and health problems in many countries, this study aimed to detect the factors influencing the increase in CIMT in opium consumers.
Methods: This cross-sectional study was conducted on 350 participants of the phase 2 of the KERCADRS cohort study who visited Besat clinic in Kerman and were divided into addicted and non-addicted groups. The participants in both groups underwent carotid artery ultrasound, and the Philips IU22 ultrasound machine was used to measure the CIMT.
Findings: The mean age of the participants was 42.28 ± 12.58 in the addicted group and 35.99 ± 15.38 in the non-addicted group ($P = 0.001$). CIMT was similar in the two groups ($P = 0.170$). Moreover, CIMT had a significant positive correlation with age, waist circumference, systolic blood pressure (SBP), body mass index (BMI), fasting plasma glucose (FPG), and triglyceride in both addicted and non-addicted groups. Age, weight, waist circumference, SBP, and BMI in the multivariate model were significant determinants of CIMT in the addicted group.
Conclusion: The results revealed that age, weight, waist circumference, SBP, and BMI were the factors influencing intima thickness in opium consumers, and no significant relationship was observed between addiction to opium and CIMT.
Keywords: Carotid intima-media thickness, Diabetes, Dyslipidemia, Hypertension, Opium addiction

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Introduction

Iran is located on the route of opium transit because of its proximity to Afghanistan. Opioid dependency in Iran is highly prevalent due to cultural acceptance.[1] Morphine is the most important alkaloid in opium poppy, but this plant has about 80 different compounds that affect metabolic and endocrine systems and can differ from pure morphine.[2,3] Since morphine relieves pain in cardiovascular patients, some people believe opium has a protective effect against cardiovascular diseases and consider it a way to treat cardiovascular diseases and diabetes.[4]

Atherosclerosis has an essential role in causing cardiovascular diseases, and measuring carotid intima-media thickness (CIMT) is one of the indicators for determining the risk of atherosclerosis in vessels, and its increase is one of the strongest predictors of cardiovascular events.[5,6]

Various studies have reported that addiction to opium does not decrease cardiovascular disease risk factors such as hyperlipidemia, diabetes mellitus, and hypertension. [7] Some reports are available on the role of opium addiction in causing heart attacks at a younger age and increasing hospital mortality.[4,8,9] In Hamziee-Moghadam and colleagues' study on 47 opium addicts and 47 healthy controls, the mean CIMT in opium

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addicts was significantly higher than in healthy controls.[10] In Saadatnia and colleagues' study, opium addiction had no significant relationship with maximum CIMT.[11] Given the contradictory results of previous studies, it is necessary to conduct research in the general population with a larger sample size to investigate the relationship between opium addiction and CIMT.

Accordingly, this study evaluated the association between opium addiction and CIMT as a marker of atherosclerosis. It also examined the association between opium abuse and other cardiovascular diseases risk factors such as hyperlipidemia and diabetes mellitus.

Methods

The present cross-sectional study was conducted on 350 participants of the Kerman Coronary Artery Disease Risk Factor Study (KERCADRS).

The participants in this study were selected in the second phase of the KERCADRS in 2017 and 2018 from among those aged 15 to 75 years. Patients with untreated hypertension, subarachnoid hemorrhage, cerebrovascular events, and cerebral hemorrhage were excluded from the study. The objectives and methods of the study were explained accurately to all participants before completing the questionnaire and performing the ultrasound. Sampling continued until the predetermined sample size was obtained in the opium-addicted and non-addicted groups. The participants were included in the two groups based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) criteria for addiction.

After obtaining informed consent from the participants, the questionnaires were completed to gather demographic information such as age, gender, smoking status, as well as the history of hyperlipidemia, cardiovascular diseases, diabetes, and use of blood-sugar-lowering drugs.

The anthropometric data (height, weight, and waist circumference) were measured. The height was measured in the standing position without wearing shoes with a 0.5-cm error from the heel to the head, and the weight was measured without wearing shoes or extra clothes with a 100-g error. The waist circumference was measured in the standing position at the space between the last rib and pelvic crest, keeping the space of 20-30 cm between the feet. The body mass index (BMI) of the participants in the study was calculated by dividing weight (kg) by the square of height (m^2).

The blood pressure was measured based on WHO guidelines after 10 minutes of rest in two turns from the right hand in the sitting position, and the mean measured values were recorded. Blood samples were taken after 12-14 hours of fasting and maintained at room temperature, and fasting plasma glucose (FPG) and serum lipids (including triglyceride, HDL, and cholesterol) were measured by enzymatic method.

DSM-IV TR criteria were used to detect addiction. According to DSM-IV TR, opium addiction is defined as a maladaptive pattern of opium use that results in clinical impairment or distress as evidenced by the presence of at least three of the seven known criteria in the last 12 months.

The participants underwent bilateral carotid Doppler ultrasound, and a Philips IU22 ultrasound machine was used to measure the CIMT. Besides, intima-media thickness was measured with a high-resolution B-mode ultrasound scanner. The thickest point of the carotid intima-media was identified by ultrasound using the common carotid artery, carotid bulb, and internal carotid artery on both sides of the neck at continuous angles. The intima-media thickness was defined based on the distance between the intima lumen edge and the advantis intima edge. The mean right and left intima-media thickness was considered as intima-media thickness.

Sample size estimation

Adibi et al reported the mean CIMT as 0.23 ± 0.77 in people with abnormal coronary angiography and 0.14 ± 0.68 in people with normal coronary angiography.[12] The minimum sample size required in the present study was calculated as 99 participants in each group using the mentioned values and considering the power of 0.9 and alpha of 0.05.

Statistical analysis

The data in the present study were analyzed using SPSS software (SPSS Inc., Chicago, IL). Qualitative data were reported as number and percentage and quantitative data as mean and standard deviation. The chi-square test was used for comparing qualitative variables between the two groups. Kolmogorov-Smirnov statistical test was used to analyze the distribution of the quantitative variables. Independent samples *t* test was also used for comparing quantitative variables between the two groups if the variable distribution was normal and Mann-Whitney statistical test was used if the distribution was abnormal.

The correlation between continuous variables was investigated using Pearson and Spearman correlation coefficient tests based on the normal or abnormal distribution of variables, respectively (according to Kolmogorov-Smirnov statistical test results).

Initially, the variables were analyzed in a univariate model, and *P* values less than 0.2 were entered into a multivariate model. Then, the highest *P* value was detected to reach all the variables less than 0.05.

Results

This cross-sectional study was conducted on 350 individuals. The mean age of addicted patients (42.28 ± 12.58) was significantly higher than that of the non-addicted patients (35.99 ± 15.38) ($P = 0.001$). The number of females was 48 (43.6%) in the addicted group and 164 (68.2%) in the non-addict group suggesting a significant difference ($P<0.001$). Systolic blood pressure (SBP) was significantly higher in the addicted group than in the non-addicted group ($P=0.023$), but there was no significant difference between the two groups ($P=0.960$) in diastolic blood pressure (DBP).

Based on biochemical tests, low-density lipoprotein (LDL) and cholesterol levels were significantly higher in the addicted group compared to the non-addicted group ($P=0.011$ and $P=0.011$, respectively). The mean CIMT was 0.51 ± 0.13 mm in the addicted group and 0.54 ± 0.14 mm in the non-addicted group, showing no significant difference between the two groups ($P=0.170$) (Figure 1). Demographic and biochemical characteristics of the addicted and non-addicted groups are shown in Table 1.

The correlation between quantitative variables and IMT in addicted and non-addicted groups was evaluated separately (Table 2). The Spearman correlation coefficient was used to evaluate the correlation between CIMT and age, SBP, and FPG in the non-addicted group due to their abnormal distribution. For other cases, the Pearson correlation coefficient test was utilized.

The results of data analysis showed CIMT had a significant positive correlation with age, waist circumference, SBP, BMI, FPG, and triglyceride in both addicted and non-addicted groups (Table 2).

Age (Adjusted β: 0.006, $P<0.001$), waist circumference (Adjusted β: 0.004, $P<0.029$), BMI (Adjusted β: 0.01, $P<0.001$), weight (Adjusted β: 0.003, $P=0.005$), and SBP (Adjusted β: 0.001, $P=0.019$) in the multivariate model were significant determinants of CIMT in the addicted group (Table 3).

Discussion

The main finding of the present study was that opium addiction had no protective effect against atherosclerosis; however, it increased LDL, cholesterol levels, and SBP in addicted people. In addition, the results of this study showed CIMT had a significant relationship with age, waist circumference, fasting blood sugar (FBS), SBP, and BMI in addicted and non-addicted groups, with the highest relationship with age.

In some societies, people believe opioids have a protective effect against cardiovascular diseases and consider opium as a treatment for some cardiovascular diseases risk factors such as diabetes and blood pressure.[13] However, in a cross-sectional study, opium use was considered a risk factor for coronary artery involvement, and opium use rate had a relationship with the severity of arteries atherosclerosis.[14] In contrast to previous studies, the cholesterol and LDL levels in the present study were significantly higher in the addicted group.[15,16]

In epidemiological studies, LDL has been proven as a marker of coronary heart disease (CHD). However, in 50% of patients with CHD, LDL has normal values. The study by Tanaka et al showed when LDL is less than 120 mg/dl, the LDL-C/HDL-C ratio is a predictor of acute myocardial infarction and sudden death.[17] Several studies have shown a significant relationship between CIMT and LDL,[18,19] but this relationship has not been observed in some studies.[20,21] In the study by Vijayasarathi and Goldberg, there was no significant correlation between CIMT and LDL, but a significant negative correlation was found between CIMT and HDL.[20] In the present study, although cholesterol and LDL levels were different between the two groups and were higher in the addicted people, higher CIMT correlated with high triglycerides. In the multivariate regression model, there was no

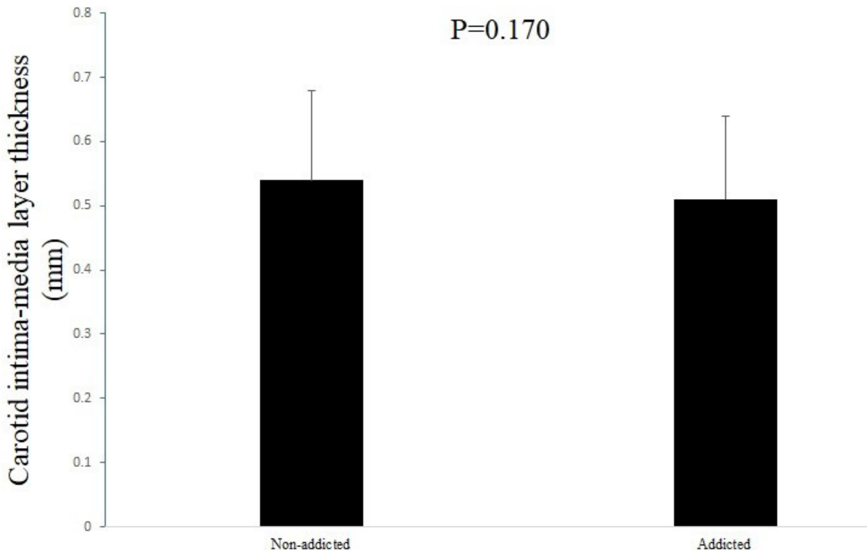

Figure 1. Comparison of mean CIMT between addicted and non-addicted groups

Table 1. Demographic and biochemical characteristics

Variable		Non-addicted group (n = 240)	Addicted group (n = 110)	*P*
		No. (%) / Mean ± SD		
Gender	Male	76 (31.8)	62 (56.4)	< 0.001*
	Female	164 (68.2)	48 (43.6)	
Age (y)		35.99 (15.38)	42.28 (12.58)	0.001*
History of hyperlipidemia	Yes	55 (22.9)	23 (21.9)	0.870
	No	185 (77.1)	82 (78.1)	
History of cardiovascular diseases	Yes	18 (7.3)	12 (11)	0.350
	No	222 (92.7)	97 (89)	
History of use of blood-sugar-lowering drugs	Yes	38 (16)	19 (17.2)	0.715
	No	202 (84)	91 (82.8)	
History of diabetes	Yes	45 (18.8)	20 (18.2)	0.863
	No	195 (81.2)	90 (81.8)	
Smoking status	Yes	4 (1.8)	101 (91.8)	< 0.001*
	No	236 (98.2)	9 (8.2)	
Weight (kg)		72.36 (14.08)	75.1 (16.75)	0.190
Waist circumference (cm)		91.9 (13)	93.05 (12.88)	0.511
SBP (mm Hg)		109.31 (17.79)	114.88 (17.97)	0.023*
DBP (mm Hg)		73.48 (10.12)	73.54 (10.54)	0.960
FPG (mg/dL)		97.05 (29.94)	102.53 (44.21)	0.280
Cholesterol (mg/dL)		171.3 (38.42)	183.83 (39.89)	0.011*
Triglyceride (mg/dL)		133.47 (62.67)	144.69 (69.27)	0.200
HDL (mg/dl)		47.41 (10.08)	46.9 (9.29)	0.690
LDL (mg/dL)		97.11 (32.99)	107.98 (30.08)	0.011*
BMI ((kg/m^2)		26.2 (4)	25.3 (5)	0.160
Duration of opium use (year)		-	12.01 ± 8.59**	-
CIMT (mm)		0.54 ± 0.14	0.51 ± 0.13	0.170

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; CIMT, carotid intima-media layer thickness.
* The difference is significant $P < 0.05$.
** It has been reported only in the addicted group.

Table 2. The correlation between quantitative variables and CIMT

Variable	Non-addicted group				Addicted group	
	Pearson correlation coefficient	*P*	Spearman correlation coefficient	*P*	Pearson correlation coefficient	*P*
Age (year)	-	-	0.563	0.000*	0.601	< 0.001*
Weight (kg)	0.134	0.162	-	-	0.168	0.079
Waist circumference (cm)	0.242	0.011*	-	-	0.339	< 0.001*
SBP (mm Hg)	-	-	0.286	0.002*	0.443	< 0.001*
BMI (kg/m^2)	0.124	< 0.001*	-	-	0.158	0.001*
FPG (mg/dL)	-	-	0.199	0.037*	0.379	< 0.001*
Cholesterol (mg/dL)	0.153	0.111	-	-	0.058	0.545
Triglyceride (mg/dL)	0.31	0.001*	-	-	0.203	0.033*
HDL (mg/dL)	-0.008	0.932	-	-	-0.175	0.068
LDL (mg/dL)	0.081	0.403	-	-	0.06	0.532
Opium consumption duration (year)	-	-	-	-	0.177	0.074

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; CIMT, carotid intima-media layer thickness.
*The difference is significant $P < 0.05$.

Table 3. The relationship between CIMT and other variables in the addicted group

Variable	Univariate		Multivariate	
	β	*P* value	β	*P* value
Gender				
Female	Ref	-	-	-
Male	0.07	0.001		
History of hyperlipidemia				
No	Ref	-	-	-
Yes	0.09	0.003		
History of cardiovascular diseases				
No	Ref	-	-	-
Yes	0.09	0.010		
Smoking status				
No	Ref	-	-	-
Yes	0.02	0.550		
Weight	0.002	0.025	0.003	0.005
Waist circumference	0.004	<0.001	0.004	0.029
SBP	0.003	<0.001	0.001	0.019
DBP	0.004	<0.001	-	-
FPG				
Diabetic	Ref	-	-	-
Non-diabetic	0.11	<0.001		
Cholesterol (mg/dL)	0.046	0.097	-	-
Triglyceride (mg/dL)	0.033	0.327	-	-
HDL (mg/dL)	-0.003	0.047	-	-
LDL (mg/dL)	<0.001	0.730	-	-
Age (year)	0.006	<0.001	0.006	<0.001
BMI (kg/m^2)	0.004	0.156	0.01	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; BMI, body mass index; LDL, low-density lipoprotein.
*The difference is significant $P<0.05$.

relationship between CIMT and hyperlipidemia, and the correlation between high triglyceride and CIMT also disappeared. In the study by Bayani et al, there was no relationship between serum lipids in addicted and non-addicted diabetic patients who had a heart attack.[22] Shirani and colleagues' study on coronary artery bypass graft candidates showed no significant difference between serum lipid profile levels in addicted and non-addicted groups.[23] However, Asgary et al showed that HDL level was lower in the group addicted to opium.[24] In the study by Rahimi et al, the frequency of low HDL levels in addicted people was significantly lower than in non-addicted people; however, no significant difference was observed between the two groups in other lipid profile parameters.[25] In the study by Gozashti et al, HDL and cholesterol levels in addicts were significantly lower than in the control group.[26]

In the present study, addicted people had significantly higher SBP. In most studies, a reduction in blood pressure has been observed in addicted people, and the vasodilation mechanism has established opium's effect in reducing blood pressure. However, in previous studies, opium addiction has generally increased the risk of cardiovascular diseases despite reducing blood pressure.[3,4,14] It has also been observed that opium dependence significantly reduces the age of myocardial infarction and sudden cardiac death. [9] In the current study, in univariate and multivariate models, the relationship between SBP and CIMT remained significant, showing the importance of this factor in CIMT and causing atherosclerosis. No significant relationship was observed between the opium use duration and CIMT. Asgary et al showed an increase in atherosclerosis risk factor in opium-addicted patients, and prolonged opium use was expected to exacerbate atherosclerosis.[24]

Although some atherosclerosis risk factors, including LDL, cholesterol, and SBP were significantly higher in the opium addict group, CIMT was not significantly different between the two groups. One of the reasons for not observing a significant difference between CIMT in two addicted and non-addicted groups could be other factors that can influence CIMT. In addition, there was no significant relationship between hyperlipidemia and CIMT in the multivariate regression analysis in the addicted group.

Schultz and Gross showed that the consumption of opium through the activation of specific receptors can reduce the pain and size of cardiac infarct in experimental animals and thus cause cardioprotective effects. [27] However, based on human studies, opium use does not reduce cardiovascular events, and in a review study, the effect of opium on exacerbating cardiovascular problems was highlighted.[4,7,28] In the present study, like Shirani and colleagues' study,[23] no significant relationship was observed between opium addiction and CIMT, and opium addiction did not reduce the risk of atherosclerosis in the carotid artery.

In the multivariate regression model, weight, waist circumference, SBP, age, and BMI maintained their significant relationship with the increase in CIMT. In the study by Beşir et al, age was reported as the only independent factor of CIMT.[29]

The relationship of the increase in waist circumference and metabolic syndrome with CIMT has also been established.[30] Metabolic syndrome includes a collection of cardiovascular risk factors and increases the risk of atherosclerosis diseases. Besides, its higher prevalence has been observed in addiction to opium.[31] A significant relationship was also observed between FBS and CIMT, consistent with other studies.[32,33]

One of the limitations of the present study was its cross-sectional nature. In cross-sectional studies, the time relationship between exposure and outcome cannot be determined because both occur at the same time. Therefore, other studies, such as clinical trials, are needed to examine the relationship between exposure and outcome. Considering the ethical limitations of conducting clinical trial studies on opium addiction, it is recommended to conduct cross-sectional studies with a larger sample size to investigate the relationship between opium addiction and CIMT. Another limitation of the present study was the relatively low age of the participants, which can be the reason for not observing a significant difference between CIMT in addicted and non-addicted people.

Conclusion

In this study, no significant relationship was observed between addiction to opium and CIMT. Nevertheless, other cardiovascular risk factors such as SBP, waist circumference, age, and BMI had a significant relationship with CIMT in the addicted group. Besides, higher levels of LDL, cholesterol, and SBP were observed in addicted people.

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Authors' Contribution

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Supervision: Ahmad Enhesari, Hamid Najafipour, Mohammad Hossein Gozashti.
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Visualization: Amir Baniasad, Mohammad Javad Najafzadeh, Roohollah Abasnia.
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Writing–review & editing: Mohammad Hossein Gozashti, Hamid Najafipour, Ahmad Enhesari, Amir Baniasad, Mohammad Javad Najafzadeh, Roohollah Abasnia, Shahin Narouee Nosrati.

Competing Interests

The authors have no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The ethics committee of Kerman University of Medical Sciences reviewed and approved the study protocol (ethic code IR.KMU.REC.1396.2172). All participants in the study provided informed consent.

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