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The Relationship between Opium Addiction and the Severity of Atherosclerosis, Lipid Profile, Inflammatory Cytokines, and Renal Function in Non-diabetic Patients Subjected to Angiography

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ABSTRACT

Background: Despite traditional beliefs about the beneficial effects of opium use, current evidence suggests an adverse effect of this substance on cardiovascular disease (CVD) risk factors. The present study aimed to investigate the association between opium-addiction status and lipid profile, the severity of atherosclerosis (measured by Gensini score), inflammatory cytokines, and renal function among non-diabetic patients subjected to angiography.

Methods: This cross-sectional study was conducted on 95 post-angiography patients. Routine tests including lipid profile, blood urea, creatinine, and hematocrit were collected at the time of admission. Also, serum levels of IL-6 and IL-8 were measured using ELISA. Independent sample t-test, Mann-Whitney U test, and chi-square were used to compare variables according to opium addiction. Multivariate regression was conducted to adjust the effect of potential confounding variables.

Results: Opium-addict subjects had a higher IL-6 (P=0.049) level and PLT number (P=0.005). In contrast, there was a lower level of TG (P=0.015) and GFR (P=0.039) in the opium-addict group. There was no association between opium addiction and other variables (P>0.05).

Conclusion: Although no significant association was observed between addiction and atherosclerosis and even there was a lower level of TG in addict subjects, there was a direct association between the serum IL-6 levels (an important inflammatory cytokine with adverse effects on coronary artery disease) and opium addiction. It has been revealed that confounding variables affect the relationship between opium use and CVD outcomes. Therefore, well-designed prospective studies controlling a vast range of general variables seem to be necessary.

Keywords: Opium, Atherosclerosis, Cardiovascular Diseases, Inflammation, Lipoproteins

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Introduction

Cardiovascular disease (CVD) is a series of heart- or vascular-related consequences that include coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism. The prevalence of CVD has been increasing in recent years. According to reports, the incidence of new cases of this disease in different countries is approximately more than 1000 people per 100,000 population, while the prevalence rate was estimated at 6500 per 100000 inhabitants (1). Dyslipidemia, smoking, blood pressure, diabetes, obesity, waist circumference, lifestyle (diet and physical activity), age, gender (higher risk in males), and socioeconomic status are among the most important predictors of CVD (2, 3). It has been revealed that the risk of CVD mortality will increase twice with smoking (4). Smoking cessation is the most cost-effective strategy in the prevention of CVD, regardless of the length or severity of the smoking habit. Smoke cessation has both immediate and long-term beneficial effects (5).

Papaver somniferum L. is the oldest plant used for medicinal or recreational purposes. The opium extracted from poppy latex has the second rank of drug abuse after cannabis in the world (6). Moreover, it is the most substance abused after tobacco in the middle east (7). Numerous studies in recent years have examined the effects of opioids on health status. Despite traditional beliefs about the beneficial effects of opium use on diabetes mellitus, hypertension, and dyslipidemia, current evidence suggests an adverse effect of these substances on CVD risk factors (8). In a large cohort study with 50045 participants, there was a dose-response association between the duration of opium consumption and CVD mortality (9). However, there are some controversies about the association between opium use and some cardiovascular implications (6). Also, there are many discrepancies in the mechanisms of the opium effect on CVD in human studies (10). It has been proposed that opium increases CVD risk by causing inflammation and oxidative stress, inducing thrombosis, and resulting in the hyperplasia of vascular smooth cells (6). Increasing evidence shows that opium addiction is associated with higher pro-inflammatory markers such as C-reactive protein (CRP) (11), hs-CRP (12), interferon-gamma (IFN-γ) (12, 13), interleukin-6 (IL-6) (14), IL-17 (12), complement factors (C3 and C4) (12), and lower anti-inflammatory mediators as IL-4 (13) and IL-1Ra (15). However, some studies have found inconsistent results that warrant more studies in this regard. In some studies, no association was observed between addiction and IL-10 (13), IL-6 (15), tumor necrosis factor-alpha (TNF-α) levels (13). On the other hand, some studies found an increase in anti-inflammatory factors (such as IL-10) in addict subjects (12). Also, it has been found that the association between opium addiction and CVD may be affected by diabetes status (16). Diabetes is one of the important risk factors for vascular disease. Addiction has also been linked to an increased chance of developing diabetes (17).

Therefore, it is necessary to show the effects of addiction on CVD independently of diabetes. Further study in this area will help to clarify the existing contradictions. In addition, identifying high-risk groups can provide the conditions to prevent more severe consequences. The present study aimed to investigate the association between opium-addiction status and lipid profile, the severity of atherosclerosis, inflammatory cytokines, and renal function among non-diabetic patients subjected to angiography.

Materials and Methods

The present cross-sectional study was conducted on 95 patients admitted in the post-angiography ward of Shafa Hospital, Kerman, Iran in 2017. Data of non-diabetic patients subjected to the angiography who was willing to collaborate in the study were collected. People with diagnosed chronic diseases such as diabetes, immune system dysfunction, renal or respiratory disease were not included in the study. The protocol of the study was approved by both Medical Ethics Committees of Kerman University of Medical Sciences.

General characteristics including age, educational status, residence area, medication use, history of hypertension (HTN), familial history of CVD in first-degree relatives, smoking status (at least 5 cigarettes/week was considered as a smoker), and opium use were collected by face-to-face interview using an experienced observer. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) criteria were used to confirm opium addiction (18). A Seca scale and stadiometer were used to measure the weight and height of the participants. In the case of inability to stand, weight was assessed using the under-bed weighing scale, and length was measured. Measurements were performed with minimal clothing and without shoes with the accuracy of 100 g and 0.1 cm for weight and height, respectively. Body mass index (BMI) was calculated by dividing weight by squares of height. Data of blood pressure and routine tests including lipid profile (triglyceride (TG), total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C)), blood urea, creatinine (Cr), and platelet (PT) number were collected from recorded information at the time of admission. Glomerular filtration rate (GFR) was calculated using modification of diet in renal disease (MDRD) equation (19). Also, serum levels of IL-6 and IL-8 were measured using enzyme-linked immunoassay (ELISA) using R&D systems kits (R&D Systems, Wiesbaden, Germany). For this, 5 cc of antecubital venous blood was collected at the time of admission, centrifuged for 10 minutes at 4000 rpm at room temperature, and isolated serum was stored at -70° C until the biochemical analysis.

The degree of stenosis was estimated by an expert cardiologist in angiography (20). Subjects were divided based on the number and percent of arteries involvement and then the severity of stenosis was assessed using the Gensini score. The Gensini instrument has a horizontal and two vertical axes that determine the degree of stenosis of each artery. To calculate the Gensini score the percentage of involvement in each artery was estimated in angiography and then the score assigned in the horizontal axis multiplied to the score of the vertical column to obtain the Gensini score for that artery. Finally, the scores of all arteries were added together to compute the total Gensini Score. Gensini score ≤20 was considered as mild coronary artery involvement and >20 was considered as severe involvement. Also, the left ventricular ejection fraction was measured during coronary angiography.

Statistical analyses

The Kolmogorov-Smirnov test was used to assess the normality of quantitative variables. Normally distributed and non-normal distributed variables are presented as mean (SD) and median (IQR), respectively. Qualitative variables are reported as frequency (%). To compare quantitative variables according to the opium addiction status or atherosclerosis severity the independent samples t-test or Mann-Whitney U-test was used. The relationship between qualitative variables was assessed by the chi-square test. Multivariate linear regression was used to estimate the unstandardized β (SE) between opium addiction and Quantitative variables. Also, logistic regression was used to estimate OR (95% CI) in the relationship between opium addiction and the severity of atherosclerosis. In model 1 (crude model) no confounding variables were entered. In model 2, the effect of gender, smoking, and BMI were adjusted. In model 3, education and history of HTN were added to the previous variables. The use of atorvastatin, chest pain, and HTN medications adjusted other than previous variables in model 4. Data were analyzed using SPSS software version 25 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY). P-values <0.05 were considered as statistically significant.

Results

Study population characteristics

Totally, 95 patients (60 males and 35 females) admitted to the post-angiography ward with a mean age of 55.58 ± 10.38 years were analyzed in the present study. The mean BMI was 24.69 ± 4.82 Kg/m^2 in the total population. About 14% of participants were smokers, 26.3% were rural, 66.3% were under diploma, and 20% had a familial history of CVD. Forty subjects (42.1%) were opium-addict and 36 ones (37.9%) had a Gensini score >20. Table 1 compares the general characteristics of subjects according to opium addiction and severity of coronary artery stenosis (Gensini score ≤20 or >20). The ratio of opium addiction was higher in males (P<0.001) and smokers (P=0.013). Also, addict subjects had a higher height (P=0.004) and a lower BMI (P=0.004). Comparing subjects according to Gensini score categories showed a more severe condition in females (P=0.008). Moreover, the height of participants in the >20 Gensini score group was significantly higher compared to the ≤20 group (P=0.009).

Table 1. Demographic characteristics of the participants according to the opium addiction status

Variable [1]		Total	Opium addiction		P-value[2]	Gensini score		P-value[2]
			Yes	No		≤20	>20	
Gender	Male	60 (63.2)	34 (85.0)	26 (47.3)	<0.001	28 (47.5)	7 (19.4)	0.008
	Female	35 (36.8)	6 (15.0)	29 (52.7)		31 (52.5)	29 (80.6)	
Education status	Under diploma	63 (66.3)	31 (77.5)	32 (58.2)	0.078	43 (72.9)	20 (55.6)	0.131
	Diploma or higher	32 (33.7)	9 (22.5)	23 (41.8)		16 (27.1)	16 (44.4)	
Residence area	Rural	25 (26.3)	12 (30.0)	13 (23.6)	0.646	13 (22.0)	12 (33.3)	0.330
	Urban	70 (73.7)	28 (70.0)	42 (76.4)		46 (78.0)	24 (66.7)	
Familial history of CVD	Yes	19 (20.0)	32 (80.0)	44 (80.0)	0.999	12 (20.3)	7 (19.4)	0.999
	No	76 (80.0)	8 (20.0)	11 (20.0)		47 (79.7)	29 (80.6)	
History of HTN	Yes	50 (52.6)	20 (50.0)	25 (45.5)	0.818	35 (59.3)	15 (41.7)	0.144
	No	45 (47.4)	20 (50.0)	30 (54.5)		24 (40.7)	21 (58.3)	
Smoking status	Yes	13 (13.7)	10 (25.0)	3 (5.5)	0.013	52 (88.1)	30 (83.3)	0.548
	No	82 (86.3)	30 (75.0)	52 (94.5)		7 (11.9)	6 (16.7)	
Anti-HTN drugs use	Yes	30 (31.6)	9 (22.5)	21 (38.2)	0.122	23 (39.0)	7 (19.4)	0.068
	No	65 (68.4)	31 (77.5)	34 (61.8)		36 (61.0)	29 (80.6)	
Anticoagulant drugs use	Yes	89 (93.7)	38 (95.0)	51 (92.7)	0.999	55 (93.2)	34 (94.4)	0.999
	No	6 (6.3)	2 (5.0)	4 (7.3)		4 (6.8)	2 (5.6)	
Chest pain drugs use	Yes	73 (76.8)	29 (72.5)	44 (80.0)	0.463	42 (71.2)	31 (86.1)	0.133
	No	22 (23.2)	11 (27.5)	11 (20.0)		17 (28.8)	5 (13.9)	
Atorvastatin use	Yes	71 (74.7)	34 (85.0)	37 (67.3)	0.059	41 (69.5)	30 (83.3)	0.152
	No	24 (25.3)	6 (15.0)	18 (32.7)		18 (30.5)	6 (16.7)	
Age (years)		55.58 (10.38)	56.37 (10.51)	55.01 (10.34)	0.532	54.57 (9.65)	57.25 (11.42)	0.225
Weight (kg)		68.89 (13.88)	67.07 (11.76)	70.21 (15.21)	0.278	68.16 (13.74)	70.08 (14.23)	0.518
Height (cm)		167.12 (9.93)	170.55 (8.23)	164.63 (10.38)	0.004	165.06 (9.92)	170.50 (9.12)	0.009
BMI (kg/m^2)		24.69 (4.82)	23.02 (3.49)	25.90 (5.30)	0.004	25.09 (5.24)	24.03 (4.03)	0.302

[1] Quantitative variables are presented as mean (SD) and qualitative variables are presented as frequency (%)
[2] P-value is calculated using independent sample t-test or chi-square for quantitative or qualitative variables, respectively
CVD: cardiovascular disease, HTN: hypertension, BMI: body mass index

The association between atherosclerosis severity and opium addiction

As presented in table 2, independent sample t-test or Mann-Whitney U-test found no difference in the Gensini score, ejection fraction, systolic blood pressure (SBP), and diastolic blood pressure (DBP) according to opium addiction status. Moreover, as shown in table 3 despite a higher frequency of Gensini score >20 and ≥1 artery involvement in opium-addict subjects, no significant association was observed in the chi-square test (P=0.134 and 0.141, respectively). In the multivariate regression model (tables 4), there was no association between opium addiction and Gensini score, ejection fraction, SBP, DBP, and angiography resulted in crude model or adjusted for confounding variables.

Table 2. Comparing quantitative variables across opium addiction status

Variable [1]	Opium addiction		P-value[2]
	Yes	No	
Ejection fraction (%)	48.12 (9.17)	49.81 (9.07)	0.374
Gensini score	14.75 (38.25)	5.00 (40.50)	0.106‡
SBP (mmhg)	120.0 (13.75)	110.0 (15.00)	0.856‡
DBP (mmhg)	70.0 (20.00)	70.0 (15.00)	0.665‡
IL-6 (pg/ml)	20.05 (61.61)	2.34 (42.99)	0.212‡
IL-8 (pg/ml)	37.16 (36.68)	34.28 (32.56)	0.753†
IL-6/BMI ratio	0.83 (3.08)	0.09 (1.54)	0.077‡
PLT	209.77 (70.96)	253.01 (72.23)	0.005
Total cholesterol (mg/dl)	138.90 (32.77)	152.92 (46.43)	0.105
TG (mg/dl)	104.17 (45.64)	138.16 (86.23)	0.015
HDL-C (mg/dl)	43.60 (11.94)	40.96 (9.84)	0.242
LDL-C (mg/dl)	74.64 (30.44)	84.85 (39.4)	0.176
GFR (mL/min/1.73 m^2)	73.42 (17.31)	83.74 (30.49)	0.039
Urea (mg/dl)	34.35 (12.85)	33.98 (8.37)	0.745
Cr (mg/dl)	1.10 (0.17)	1.10 (0.30)	0.629‡

[1] Normal distributed variables are presented as mean (SD) and non-normal variables are presented as median (IQR)
[2] P-value is calculated using independent sample t-test (log-transformed variables are noted by †) or Mann-Whitney U-test (noted by ‡)
SBP: systolic blood pressure, DBP: diastolic blood pressure, IL: interleukin, PLT: platelet, TG: triglyceride, HDL-C: high-density lipoprotein, LDL: low-density lipoprotein, GFR: glomerular filtration rate, Cr: creatinine

Table 3. Comparing Gensini score categories and angiography results according to opium addiction status

Variable [1]		Opium addiction		P-value[2]
		Yes	**No**	
Gensini Score	< 20	21 (52.5)	38 (69.1)	0.134
	≥ 20	19 (47.5)	17 (30.9)	
Angiography results	No arteries involved	13 (32.5)	27 (49.1)	0.141
	≥ 1 artery is involved	27 (67.5)	28 (50.9)	

[1] variables are presented as frequency (%)
[2] P-value is calculated using chi-square test

Table 4. The association between quantitative variables and opium addiction using multivariate linear regression

Variable[1]	Model 1[2]		Model 2[3]		Model 3[4]		Model 4[5]	
	β (SE)	**P-value**	**β (SE)**	**P-value**	**β (SE)**	**P-value**	**β (SE)**	**P-value**
Ejection fraction (%)	-1.69 (1.89)	0.374	-1.42 (2.15)	0.511	-1.26 (2.23)	0.572	-1.24 (2.30)	0.591
Gensini score	9.13 (5.60)	0.107	2.80 (6.15)	0.649	3.98 (6.35)	0.533	2.29 (6.52)	0.726
SBP	1.01 (5.63)	0.857	4.57 (6.37)	0.475	3.76 (6.47)	0.562	5.36 (6.56)	0.416
DBP	2.37 (5.51)	0.668	4.36 (6.27)	0.489	4.41 (6.36)	0.490	3.74 (6.36)	0.558
IL-6	6.76 (5.40)	0.214	8.96 (6.07)	0.144	10.57 (5.86)	0.076	11.86 (5.91)	0.049
IL-8	0.01 (0.14)	0.929	0.11 (0.16)	0.487	0.09 (0.16)	0.592	0.10 (0.17)	0.572
IL-6/BMI ratio	9.58 (5.35)	0.077	7.89 (5.82)	0.179	9.27 (5.63)	0.104	10.40 (5.74)	0.074
PLT	-43.24 (14.90)	0.005	-32.76 (16.87)	0.055	-32.69 (17.51)	0.065	-30.00 (18.23)	0.104
Total cholesterol	-14.02 (8.57)	0.105	-6.73 (9.58)	0.484	-4.49 (9.74)	0.646	-4.14 (10.09)	0.682
TG	-33.98 (14.97)	0.026	-38.79 (17.04)	0.025	-33.90 (17.58)	0.057	-39.78 (17.88)	0.029
HDL-C	2.63 (2.23)	0.242	6.31 (2.41)	0.011	5.14 (2.43)	0.037	4.92 (2.49)	0.052
LDL-C	-10.22 (7.49)	0.176	-5.88 (8.41)	0.486	-3.25 (8.53)	0.704	-1.63 (8.84)	0.854
GFR	-10.32 (5.36)	0.057	-3.83 (5.36)	0.477	-0.84 (5.41)	0.876	-0.005 (5.57)	0.999
Urea	-0.009 (0.026)	0.745	-0.01 (0.03)	0.704	-0.01 (0.03)	0.550	-0.02 (0.03)	0.411
Cr	2.74 (5.69)	0.632	-1.09 (5.38)	0.839	-1.57 (5.54)	0.778	-1.84 (5.78)	0.751

[1] Unstandardized β (SE) are presented from multivariate linear regression
[2] The relationship between opium addiction and dependent variable in the crude model
[3] Adjusted for the effect of gender, smoking, and BMI
[4] Adjusted for the effect of gender, smoking, BMI, education, and history of HTN
[5] Adjusted for the effect of gender, smoking, BMI, education, history of HTN, and use of atorvastatin, chest pain, and HTN medications
SBP: systolic blood pressure, DBP: diastolic blood pressure, IL: interleukin, PLT: platelet, TG: triglyceride, HDL-C: high-density lipoprotein, LDL: low-density lipoprotein, GFR: glomerular filtration rate, Cr: creatinine

The association between inflammatory cytokines and opium addiction

A preliminary comparison between addict and non-addict subjects found no difference in the serum IL-6 and IL-8 levels. However, the ratio of IL-6/BMI tends to be higher in addict subjects (P=0.077). Also, non-addict patients had a higher PLT number compared to the addict group (P=0.005).

In multivariate linear regression (table 4), there was a direct association between the serum IL-6 levels and opium addiction after adjusting for the effect of gender, smoking, BMI, education, history of HTN and use of atorvastatin, chest pain, and HTN medications in model 4 (β=11.86; SE=5.91; P=0.049). Moreover, the inverse association between PLT numbers and opium addiction lost its significance after adjusting for confounding variables in models 2, 3, and 4. No other change was observed in the results following multivariate regression.

The association between lipid profile and opium addiction

It has been revealed that opium-addict subjects have a lower TG level compared to the non-addicts (104.17 ± 45.64 VS. 138.16 ± 86.23; P=0.015). This association remained significant after adjusting for confounding variables in models 2 and 4. However, in model 3 (adjusted for the effect of gender, smoking status, BMI, education level, and history of HTN) the association lost its significance (β=-33.90; SE=17.58; P=0.057). Independent sample t-test found no association between opium addiction and serum HDL levels. However, a direct association was observed after adjusting for confounding variables in models 2 and 3. In model 4, this association was not significant after adjustment for the effect of medication use (P=0.052). No relationship was observed between opium addiction, total cholesterol, and LDL-C levels.

The association between renal function and opium addiction

As shown in table 4, opium-addict subjects had a lower GFR compared to non-addict ones (73.42 ± 17.31 VS. 83.74 ± 30.49 respectively, P=0.039). There was no difference between groups in the blood urea (P=0.745) and Cr (P=0.629) levels. In the linear regression, the association between opium addiction and GFR completely lost its significance after adjusting for confounding variables.

Discussion

The present study evaluated the relationship between opium addiction and the severity of atherosclerosis, inflammatory cytokines, lipid profile, and markers of kidney function. Although there was no association between opium addiction and the severity of atherosclerosis, some evidence suggested an increase in the serum levels of inflammatory cytokines by the use of opioids. Moreover, there were some trends for adverse effects of opium on disease severity. It has been revealed that the consequences of opioids on CVD patients may be affected by confounding variables including gender, BMI, smoking status, education levels, history of HTN, and medication use. As observed, the association between addiction and GFR was also lost by modulating the effect of these variables.

The present study did not find any association between opium addiction and the Gensini score, angiography results, or ejection fraction. Nevertheless, opium use was insignificantly associated with poor CVD outcomes. Most of the previous studies showed a relationship between opium addiction and an increase in the risk of coronary artery disease (CAD) (21-23). Moreover, in a large cohort study with more than 50000 subjects, opium consumption increased the risk of all-cause and CVD mortality (9). A study in 1925 on diabetic patients showed that there is a dose-response relationship between opium use and the Gensini score (22). At the other extreme, there are some other studies with conflicting results. A recent cohort study on 117 opium-addict and 217 non-opium-addict patients presenting ST-elevation myocardial infarction found no association between opium use and cardiovascular adverse outcomes (24). Also, in a study with 1339 candidates of coronary bypass graft, it has been reported that opium addiction does not decelerate atherosclerosis of carotid arteries (25). The present study found no association between ejection fraction and opium addiction. This was in line with the previous studies (24, 26, 27). It appears that the adverse effects of opium may be affected by the history of previous chronic diseases. As mentioned earlier, opium can aggravate atherosclerosis in diabetic patients (22). The present study was conducted in non-diabetic patients. Another important factor in this relationship is the concurrent tobacco use in opium-addict subjects. Based on previous studies and the present study, cigarette smoking is more prevalent in opium users (24). Smoking is an independent factor in CVD and its rate of consumption can affect the severity of atherosclerosis (24, 28). However, adjusting for the effect of smoking status did not change the relationship between opium use and the severity of CAD. In addition, recent studies demonstrated that 20-50% of patients with angina have normal arteries in angiography. It has been suggested that coronary microvascular dysfunction (CMD) may be involved in these patients (29). Although there are few studies in this area, there is evidence of an independent effect of opioid use on CMD (30). So, angiography may not completely present the outcomes of opium addiction on the risk of CVD.

Opium addiction can affect the cardiovascular system through different mechanisms. It may be associated with the TNF-α-IL-6-CRP pathway (31). Previous studies showed that opium addiction provokes oxidative stress and reduces antioxidant enzymes level (32, 33). In the present study, only there was a direct association between IL-6 and opium addiction after adjusting the effect of confounding variables. This was in line with the study of Asadikaram *et al.* (14) on lymphocyte cells. More studies showed that opium addiction increases other pro-inflammatory markers as mentioned earlier (12, 13). However, no association was found between IL-8 and opium addiction in this study. Also, the association between IL-6/BMI and opium use was evaluated, as it may be a new predictor of future adverse outcomes in CAD patients and the role of obesity on IL-6 levels (34). These conflicting results were also evident in previous studies that show a non-significant association between opium use and inflammatory markers (15) or an increase in anti-inflammatory cytokines in addicted subjects (12). Considering the important role of IL6 in the incidence of cardiovascular disease and its mortality (35), and the potential of IL6 inhibition as a novel method for vascular protection discussed in recent studies (36), further studies with more samples are warranted to address this discrepancy in the association between inflammatory markers and addiction. However, in the present study, addiction was associated with an increase in IL6.

Another discrepancy in the effect of opium addiction on CVD risk factors is related to lipid profile. Most of the studies did not find any association between opium use and TG (11, 37), total cholesterol (11, 22, 25), LDL (11, 22, 37), and HDL (22). Surprisingly, the present study found a lower TG in opium-addict subjects compared to the non-addict group. However, the levels of TG in both groups were in the normal range. A study in diabetic patients found lower cholesterol in opium-addict compared to non-addict subjects (38). This is contrary to the findings of animal studies (10). To conclude definitively, these studies should be replicated in larger human studies.

This study also evaluates the effect of opium addiction on the renal function of CAD patients. Studies showed that renal dysfunction increases the adverse effects of CVD (39). Although preliminary analyses suggested a deleterious effect of opium use on GFR, this association was disappeared after adjusting for potential confounders. A study by Rahimi *et al.* (38) did not find a significant association between GFR and opium consumption. Studies are scarce in this regard and comparison is impossible. More studies are needed to find how opium addiction affects renal function.

In summary, although there was a significant inverse correlation between addiction and TG levels and no significant correlation was found between addiction and the severity of coronary artery disease, a direct association was observed between addiction and serum IL6 levels. Therefore, considering the effect of addiction on coronary microvascular dysfunction (CMD) (29) and the effect of addiction on the increase of IL6, as a cytokine with a pathological role on cardiovascular disease, the possibility of the association between addiction and future cardiovascular events cannot be rejected.

The present study examined the unclear aspects of the opium effect on the complications of CVD. However, some limitations should be noted. The retrospective design of the study does not show the causality of the relationships. Another important limitation is that people may hide their addiction due to cultural issues. Also, there might be other confounding variables that affect the relationships. The relatively small sample size is another limitation of the study that makes the relationships statistically insignificant despite the observed differences.

Conclusion

In the present study, although opium use was associated with a decrease in the serum TG and no association was observed with the Gensini score, there was a higher serum IL-6 level, an important inflammatory cytokine involved in the pathology of the CVD, in opium-addict subjects. However, prospective large studies should confirm these results. Well-designed studies should reconsider the findings of this study about the role of opium addiction on renal function of CVD patients. In addition, the predictive effect of the IL-6/BMI ratio on adverse outcomes of CVD should be investigated in studies with a larger sample size.

Availability of data and materials

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

Ethics approval and consent to participate

The protocol of the study was approved by both Medical Ethics Committees of Kerman University of Medical Sciences

Consent for publication

Informed consent was obtained from the patients for use of their records for this study and publication.

Conflict of interests

The authors declare no conflict of interest for this study.

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