Lipid Profile in Opium Users: Results of Fasa PERSIAN Cohort Study, First Phase

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Research

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Abstract

Background: One of the main health problems in many societies is the increase of opium abuse which correlated with many problems such as cardiovascular disease. The goal of our study is to evaluate the correlation of opium use with blood lipoproteins as risk factors of CVD.

Methods: This is a cross-sectional study on participants of the first phase of the PERSIAN Cohort study who were 35 -70 years old. Demographic characteristics, history of smoking, alcohol, and opium consumption, medical history and medications were asked and checklists were filled out. level of physical activity and fat intake was registered. lipoprotein profiles were investigated by blood sampling. IBM SPSS Statistics v21 was used to analyze the correlation of opium and lipid profile and the significant level was <0.05.

Results: From 9300 participants with a mean age of 48.06±9.44 years old, 49.6% were male. About 24.1% of participants used opium. The level of total cholesterol (adjusted p= 0.02) and HDL (adjusted p= 0.04) in people who used opium was significantly lower than others. But, the level of triglyceride (p=0.11) and LDL (adjusted p= 0.06) was not different in users and non-users. LDL (OR=0.8, adjusted p= 0.009) and total cholesterol (OR=0.81, adjusted p= 0.007) had normal level in people who used opium than non-consuming people.

Conclusion: This study showed that there is correlation between opium usage and lower level of total cholesterol and LDL, however the lower level of HDL in normal range was seen in opium users.

Introduction

Due to the World Drug Report, about 58 million people of the world's adult population used one type of opium in 2018(1). Evidence showed that opium is traditionally used in many south and central Asian countries, including India, Iran, Afghanistan, and Pakistan (2).In these cultures people believe that opium usage is effective in the control of blood sugar, blood pressure, and lipids that is one of the causes of increasing the prevalence of opium usage in middle age and elderly (3). In total, the prevalence of drug abuse increasing unfortunately and addiction is being one of the important issues of the day. The prevalence of opium usage in Iran varies from 8.9%in rural areas of Babol (4) to 17% in Golestan (5) and 24.7% in the rural areas of kerman (6).

Cardiovascular, respiratory, and Central Nervous Systems are mostly affected by the usage of opium. Most studies showed that the opium usage increase risk of acute myocardial infarction, atherosclerosis and cardiovascular mortality(7). Also, opium usage increases the risk of many cancers such as lung, esophageal, gastric, laryngeal and bladder cancer (2).

Lipid profiles are known as risk factors of cardiovascular disease and many studies assessed the correlation of opium and lipid levels. Aghadavoudi et al. showed that LDL and triglyceride levels in drug addicts were higher than non-drug-dependent groups(8). In a study by Fatemi SS et al. is confirmed that

cholesterol, triglyceride and LDL-c significantly reduced in people who consumed opium compared with people who did not consume this(9). While in other studies it has been pointed out that the levels of triglyceride, total cholesterol, and LDL were significantly increased in the drug addict group, but HDL levels did not change significantly (10). There are many controversies about the effect of opium on lipid profile. To investigate the correlation of opium and lipid profile There are many confounding factors that affect, such as smoking and alcohol consumption. So, in this study correlation of opium and lipid profile was evaluated considering these confounding factors in a remarkable population with a sufficient sample size of who used opium in the Fasa cohort study.

Methods And Materials

Study design and participants

This study is a cross-sectional study as the first phase of a longitudinal Fasa branch of PERSIAN (prospective Epidemiological Research Study in Iran) cohort study on the population of Fasa, south of Iran. Geographically Fasa is a city in a southeast of Fars province with total population of about 250,000 people. One of the districts is called Sheshdeh (28°56'56.0"N53°59'26.9"E) which contain of 41,000 people was chosen for Fasa cohort study. people in the age range of 35–70 years old were invited to this study who were about 10000 people. The protocol of this population-based mega project has in presented by Malekzadeh and Farjam et al. in 2016 (11–13).

people who were using medication which affect lipid profile such as additive containing Alcohol-Isotretinoin (Accutane, Roaccutane), OCP (Estrogen, Progesterone), Methylprednisolone, Prednisolone, Betamethasone, Dexamethasone, Hydrocortisone, HDL additive and TG, Chol, LDL reducer (Atorvastatin, Lovastatin, Simvastatin, Fluvastatin, Gemfibrozil, Clofibrate, Fenofibrate, Niacin, Ezetimibe, Cholestyramine) were excluded.

Study instruments and Variables assessment: Each participant was interviewed based on questionnaire approved by the PERSIAN cohort consortium in Islamic republic of IRAN. Data gathering tools are the general information questionnaire (sex, age, marital status, education level, job records, socioeconomic status, place of living) and clinical information questionnaire (history of chronic diseases and used medications). All individuals who entered the study was evaluated for Weight, height, BMI. Blood sampling was done for every participant to check lipid Profile including Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Triglyceride (TG), Cholesterol (colorimetry, pars Azmoon kit). Abnormal level of TG, Chol, HDL and LDL were considered as 150 mg/dl, 200 mg/dl, 40 mg/dl for men and 50 mg/dl for women and 130 respectively (https://labtestsonline.org/test/lipid-panel).

History of smoking, opium and alcohol usage was taken. Participants were asked if they are active current smoker, use opium derived products or alcohol frequently in a week.

Validated Food Frequency Questionnaire (FFQ) and International Physical Activity Questionnaire (IPAQ) were filled out to evaluate fat intake (Kcal) and Physical activity (Met-min/week) of participants in this

study.

There are many confounding factors such as age, gender, BMI, Fat intake, medications, smoking and alcohol consumption that were used as confounder in regression model.

Statistical Analysis

The univariable statistical analysis was performed by using Chi square, t-test, ANOVA and Pearson correlation tests. Multivariable linear and logistic regression model analysis was done using enter selection of $p < 0.2$. IBM SPSS Statistics v21 was used and P-value < 0.005 was considered as significance level.

Results

This study was conducted on 9300 participants with mean age of 48.06 ± 9.44 years that 4340 (46.7%) of them were male. Mean years of education was 4.8 ± 3.89. Of total, 8318(89.4%) were married and 4867(52.3%) had job, (Table 1).

Table 1
Socio demographic Characteristics of the opium and non-opium users in first phase of PERSIAN cohort study

variable	Opium user		Opium non-user		Total	
	n	%	n	%	n	%
Gender						
Male	2152	49.6	2188	50.4	4340	46.7
Female	87	1.89	4873	98.2	4960	53.3
Job status						
Employed	1946	40	2921	60	4867	52.3
Unemployed	291	6.6	4125	93.4	4416	47.5
Marital status						
Single	53	14.8	304	85.2	357	3.8
Married	2163	26	6155	74	8318	89.4
widow	12	2.3	517	97.7	529	5.7
Divorced	11	11.5	85	88.5	96	1
Socio-economic Status						
Low	656	21.4	2411	78.6	3067	33
Middle	722	24.2	2262	75.8	2984	32.1
High	843	26.6	2322	73.4	3165	34
variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (Year)	47.13	8.58	48.36	9.68	48.06	9.44
Education (Years)	5.78	3.80	4.48	3.87	4.80	3.89
BMI (Kg/M^2)	23.39	4.54	26.22	4.72	25.54	4.83
Physical activity (Met-hr/day)	44.90	14.38	40.74	10.21	41.74	11.49
Fat intake (gr/day)	89.78	42.35	72.69	34.91	78.8	37.55

2564 (27.6%) people were current smoker, 2239 (24.1%) were opium users and 196 (2.1%) consumed alcohol regularly.

In this population Mean of TG was 130.88 ± 82.72, Cholesterol was 186.38 ± 38.58, LDL was 109.1 ± 32.22, and HDL was 51.06 ± 15.98 mg/dl.

Univariate analysis show that age ($r = 0.15$, $p < 0.001$), years of education ($r=-.0.11$, $P < 0.001$), BMI ($r = 0.2$, $p < 0.001$), physical activity base on MET ($r=-0.09$, $p < 0.001$), fat intake ($r=-0.05$, $P < 0.001$) were significantly correlated with cholesterol level.

Female, unemployed, and widow participants had significantly higher level of cholesterol. Triglyceride level was not correlated with Age ($r = 0.01$, $p = 0.07$), years of education ($r=-.0.01$, $P = 0.19$) and fat intake ($r=-0.009$, $p = 0.36$) but, BMI ($r = 0.21$, $p < 0.001$) and physical activity base on MET ($r=-0.05$, $p < 0.001$) were significantly correlate with TG. Female, single and divorced, low socioeconomic level participants had significantly lower level of TG.

Lower level of HDL was seen in male, married, employed and high socio-economic status participants. Age ($r = 0.08$, $p < 0.001$), years of education ($r=-0.13$, $p < 0.001$) and BMI ($r=-0.02$, $p = 0.01$) were significantly correlated but physical activity ($r=-0.01$, $p = 0.3$) and fat intake ($r = 0.005$, $p = 0.65$) were not correlated with HDL level.

Age ($r = 0.13$, $p < 0.001$), years of education ($r=-0.07$, $p < 0.001$), BMI ($r = 0.14$, $p < 0.001$), physical activity ($r=-0.08$, $p < 0.001$) and fat intake ($r=-0.05$, $p < 0.001$) were significantly correlated with LDL level. Female, widow and unemployed persons had higher level of LDL, (Table 2).

Table 2
Correlation of lipid profile and socio-demographic characteristics of participants in first phase of PERSIAN cohort study

variable	Cholesterol mean ± SD	P value	TG mean ± SD	P value	LDL mean ± SD	P value	HDL mean ± SD	P value
Gender								
Male	179.82 ± 37.22	< 0.001	136.17 ± 92.23	< 0.001	105.26 ± 31.06	< 0.001	47.28 ± 14.39	< 0.001
Female	192.3 ± 38.85		127.2 ± 74.65		112.47 ± 32.86		54.36 ± 16.56	
Job								
Employed	181.61 ± 37.9	< 0.001	142.53 ± 87.03	0.16	106.56 ± 31.47	< 0.001	48.49 ± 14.64	< 0.001
Unemployed	191.84 ± 38.68		130.14 ± 79.31		111.9 ± 32.84		53.87 ± 16.88	
Marital status								
single	183.65 ± 37.59	< 0.001	114.68 ± 69.76	< 0.001	105.23 ± 31.06	< 0.001	55.48 ± 19.81	< 0.001
Married	184.6 ± 39.06		132.43 ± 83.92		107.38 ± 32.74		50.69 ± 15.76	
divorced	193.43 ± 41.23		110.34 ± 55.92		105.99 ± 29.76		53.5 ± 17.25	
widow	181.56 ± 35.88		136.89 ± 69.53		113.3 ± 35.56		52.63 ± 14.43	
Socio-economic level								
Low	186.06 ± 40.3	0.06	126.58 ± 76.28	< 0.001	108.69 ± 33.75	0.26	51.99 ± 16.09	< 0.001
Middle	185.6 ± 39.58		133.78 ± 90.5		107.51 ± 33.35		51.3 ± 16.17	
High	183.63 ± 37.75		135.16 ± 80.13		106.76 ± 31.6		49.81 ± 15.36	
Cigarette smoking								
Yes	178.97 ± 38.74	< 0.001	133.13 ± 84.83	0.2	104.78 ± 31.55	< 0.001	47.5 ± 15.05	< 0.001

variable	Cholesterol mean ± SD	P value	TG mean ± SD	P value	LDL mean ± SD	P value	HDL mean ± SD	P value
No	189.37 ± 38.16		130.72 ± 82.86		115.78 ± 32.33		52.41 ± 16.12	
Alcohol consuming								
Yes	179.05 ± 40.4	0.006	146.21 ± 96.89	0.03	105.2 ± 35.18	0.11	43.95 ± 11.4	< 0.001
No	186.66 ± 38.56		131.05 ± 83.07		109.2 ± 32.16		51.22 ± 16.03	

Analysis show that cigarette smokers and alcohol users had significantly lower level of cholesterol compare with non-users. But alcohol consumers had significantly higher level of TG compare with non-users. LDL level was lower in cigarette smokers significantly. Cigarette smokers and alcohol users had lower level of HDL, (Table 2).

In a linear regression model, we added all variables which were correlate with lipid profile (Chol, TG, LDL, HDL) in univariate analysis with significant level of < 0.2. Adjusted p value was reported for correlation of Opium and lipid profile. Opium users had significantly lower level of total Cholesterol (β=-2.5), LDL (β=-2.03) and HDL (β=-1.0), Fig. 1.

Due to the importance of high lipid profile as risk factor for many diseases such as cardio vascular, we analyzed correlation of opium usage and abnormal level of lipid profile in present of other variable and confounders in logistics regression model, (Table 3).

Table 3
logistic regression model for lipid profile in first phase of PERSIAN cohort Study.

Variable	SE	OR	β	P value
Cholesterol	0.07	0.82	-0.19	0.008
TG	0.06	1.03	0.03	0.64
HDL	0.22	0.83	-0.18	0.41
LDL	0.08	0.78	-0.24	0.003

Discussion

This study was conducted on the rural population of Fasa PERSIAN cohort study with a mean age of 48 years old. The prevalence of opium usage was 24 people per 100 individuals. The frequency of current cigarette smoking and regular alcohol drinking was 27% and 2%, respectively. One of the considerable

causes for the high prevalence of opium abuse in this study compare to others (4, 5, 14) is the location of Fasa city in the route of transportation of opium. Mainly The route of transportation of drugs into the country from the eastern border (Kerman province) and from the southern borders (Hormuzgan province) crosses the city of Fasa. So, people have more access to this kind of substance (15).

Due to Middle Eastern societies people belief that traditionally consumption of opium is effective for control blood pressure, lipids and glucose and to prevent heart diseases (16), there are many studies with different results about opium effects on lipid profile. Some studies have suggested that opium use has no significant effect on total cholesterol, LDL, or HDL-C (17). In contrast, a study by Fatemi SS et al. is confirmed that LDL significantly reduced in people who consumed opium (9). While other studies pointed out that the levels of triglyceride, total cholesterol, and LDL were significantly increased in the drug addict group, but HDL levels did not change significantly in rabbits (10). In a systematic review and meta-analysis study on diabetic patients, results showed that total cholesterol was lower in opium abusers but no significant changes were shown in other lipid profile between users and non-users (18). Furthermore, our finding demonstrated that opium users had lower levels of total cholesterol, LDL and HDL in comparison with non-users. But opium usage had no correlation with the TG level.

The relationship between low cholesterol level and opioid signaling has been studied previously (4). Lipid rafts microdomains exist in the outer layer of the plasma membrane and contain high levels of cholesterol. Also, these microdomains host opioid receptors including μ-opioid receptor (MOR), κ opioid receptors (KOR), and δ-opioid receptors (DOR) as well as a variety of signaling factors such as G protein-coupled receptors (GPCR) (19, 20). The process of opioid signaling has many steps including desensitization, phosphorylation, internalization, and resensitization. Internalization considers as the primary step that leads to the resensitization of the opioid receptors (4). It has been reported that Cholesterol depletion reduces the internalization of δ-opioid receptors in HEK293 cells (6). According to Zheng et al., reducing the cholesterol level by simvastatin, disrupts the opioid signaling in the cultured neurons and decreases the analgesic effect of opioids in a mouse model (1). Also, a clinical study conducted by Huang et al. indicated that patients with low levels of cholesterol may require higher doses of opioids to reduce their pain (5). Taken together it seems that cholesterol has an important role in the opioid signaling.

Our result showed significantly lower levels of cholesterol among opium users. Also, we mentioned the previous studies emphasizing that low cholesterol levels impair the opioid signaling. However, the chronology of low cholesterol levels and opioid tolerance among amusers is not clear yet. Experimental and clinical studies should be conducted to determine if opium abuse causes low cholesterol levels or low cholesterol level accelerates the process of tolerance in opioid abusers? It is known that opioid abuse dramatically changes the diet and causes loss of appetite and malnutrition in most cases (3). It is possible that lack of proper diet leads to reduced cholesterol levels in the opium abusers that cause more opioid tolerance and consequently these individuals require increasing opium dose over time. However, this hypothesis requires precise studies to prove.

While, lower levels of cholesterol in opium abusers could be due to decrease of appetite and nutritional deficiency in them (21, 22), it was shown that opiate agonists by the effect of κ receptors could cause decrease of carbohydrate to fat ratio intake in rats (23). However, in our study with the inclusion of fat intake, BMI, and other confounders, a lower level of total cholesterol was seen in opium users.

The importance of serum lipid profile is known as risk factor of cardiovascular diseases. Lipids profile is one of the most important risks of metabolic syndrome and 10 years risk of cardiovascular disease. So, it is necessary to notice the correlation of opium consumption and serum lipids due to cut points that are known as hyperlipidemia in the clinic. Considering the cut point of abnormal level for serum lipids with the inclusion of other variables and confounders in the correlation of opium and lipid profile, we found that opium usage was protective for increasing the level of total cholesterol and LDL to an abnormal cut point, but not for TG and HDL. Marmor M et al showed that usage of opium or morphine could have a protective effect against cardiovascular diseases (16), which is aligned with our results. But in contrast, many studies showed that opium addiction is correlated with cardiovascular diseases (24–28), and usage of opium increase the risk of death with several causes such as circulatory diseases (29). Contradiction in results could be due to the variation in method, dosage, and duration of consumption of opium in different studies.

Maybe with more studies, the level of opium consumption due to the effect of it on lipid profile would be defined as what has been done for harmful alcohol dosage.

As the strength of our study, we can mention the elimination of many confounding factors including medication, fat intake, BMI, and physical activity. The study is a population base in a large sample of people. Also, we used one type of device and a single laboratory to measure the amount of blood lipids of all participants.

One of the limitations of our study is that the cause and effect relation between opium and lipid profile could not be shown, because of the type of study that is a cross sectional. It seems to be needed the assessment of this relation in longitudinal studies for detecting causality with consideration of dose and duration of consumption.

Conclusion

Lower levels of total cholesterol and HDL-C was seen in opium users but with consideration of abnormal cut point for lipid profiles, opium users had a normal level of LDL and total cholesterol in comparison with non-users who had abnormal levels. Despite our results, opium usage is not recommended for a decrease in lipid profile and risk of heart disease because opium has known side effects on many organs and causes other non-communicable diseases such as cancers.

Declarations

Ethics approval and consent to participate:

The study protocol was approved by National and Regional Ethics Committee of FUMS (code: IR.FUMS.REC.1396.234) and Research Board of Fasa University of medical Sciences (code: 94153). A written and informed consent was obtained from each participant to enter the first phase of cohort study.

Availability of data and materials section:

The datasets were analyzed during the study are available from the corresponding author on reasonable request.

Consent for Publication:

Not applicable

Conflict of interests:

Authors have no competing interest to declare.

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Authors' contributions:

Aided in study conceptualization. aided in study design. aided in statistical analysis of data. aided in interpretation of study results. aided preparation of final draft of manuscript. All Authors approved the final form of the manuscript.

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Figures

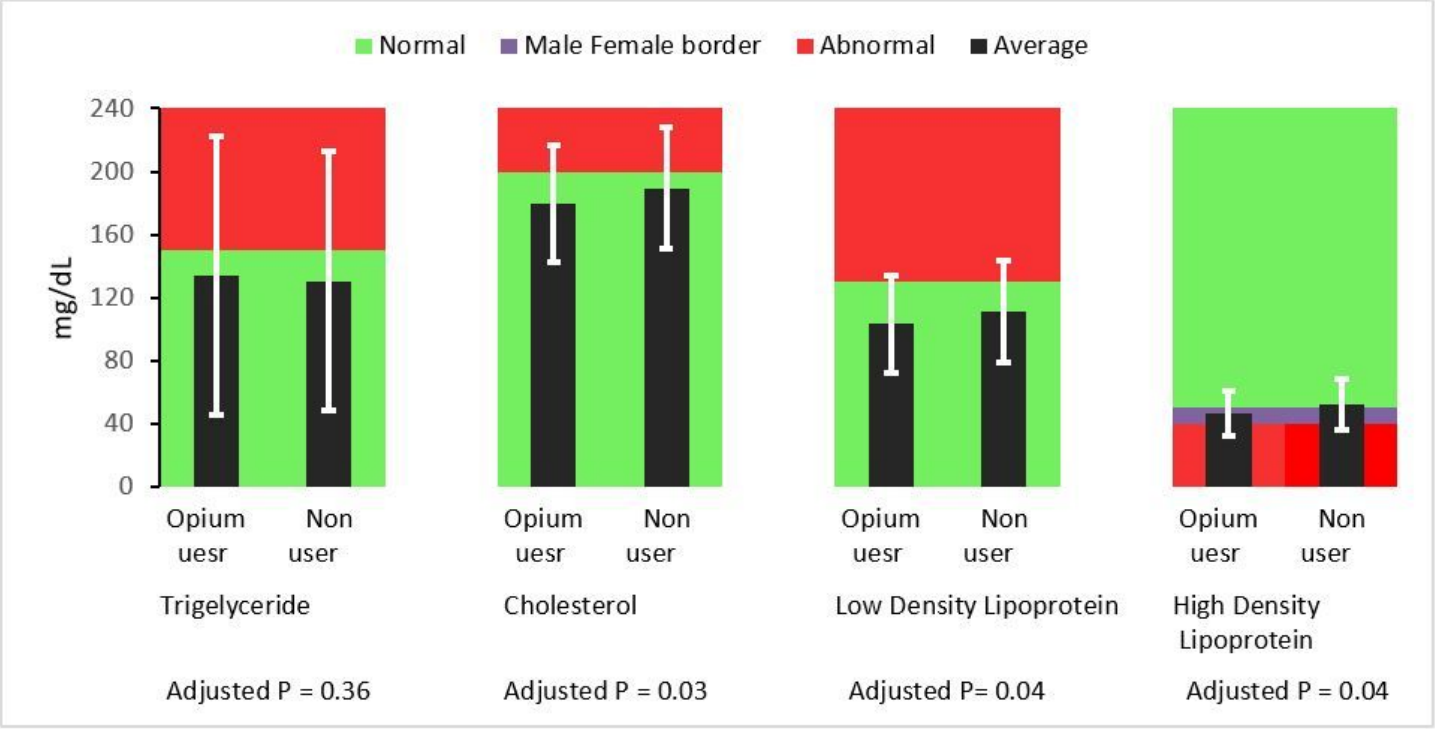

Figure 1

linear regression model for lipid profile in opium users and non-users, first phase of PERSIAN cohort Study