

Effect of Severity of Opiate Use on Cardiometabolic Profile of Chronic Opiate Dependents of Western Rajasthan

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Received: 17 April 2018 / Accepted: 24 May 2018 / Published online: 6 June 2018
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Abstract Lack of cardiometabolic profile data based on severity of opiate dependence for opiate abusers. The study aimed to evaluate the effect severity of opiate abuse on the cardiometabolic profile of male opiate abusers without comorbidities. The study included 30 healthy controls (HCs), 90 prospective chronic opiate (opium and heroin) abusers, with and without co-dependence of smoking and tobacco-chewing. The subjects were categorized based on severity of opiate dependence questionnaire (SODQ) and metabolic syndrome (MS) based on NCEP ATP-III criteria and fasting blood samples analyzed for sugar, insulin, insulin resistance (IR), lipid profile, Hs-CRP and total antioxidant capacity (TAC). There was higher prevalence of MS in opiate abusers as compared to HCs. Majority of the patients fell in grade 2 and 3 of severity. There was significant difference across groups for WHR ($p < 0.001$), SBP ($p < 0.03$), FBS ($p < 0.001$), insulin ($p < 0.02$), IR ($p < 0.03$) and TAC ($p < 0.01$). Multiple regression analysis of SODQ grades 2 and 3 independently predicted TAC by Hs-CRP ($p = 0.032$ and 0.042). There was a significant correlation of TAC with serum insulin, IR and Hs-CRP in SODQ grade 2 and serum insulin and Hs-CRP in SODQ

grade 3. Chronic opiate abuse is not benign and predisposes abusers to cardiometabolic risk with increasing severity of dependence, owing to oxidative stress and chronic low-grade inflammation.

Keywords Cardiometabolic · Opiate abuse · SODQ · Insulin resistance · Total antioxidant capacity · HsCRP

Introduction

Habitual use of opium has been documented in Indians since nineteenth century, but little attention has been paid to the chronic opiate abuse which is rampant now in many parts of the country. Opiate abuse is an important cause of premature mortality and morbidity among adults. Besides its socio-economic effects, its triggering role on disabling disorders such as cardiovascular disorders also has been suggested [1]. There is a traditional belief of opiate use having protective effects against cardiovascular disease (CVDs) and diabetes mellitus (DM). However, the reports of higher risk of coronary artery disease (CAD) among opium abusers as compared to the non-opium users suggests the opposite [2]. The data on traditional risk factor for cardiovascular risk-serum lipid profile is inconsistent in opium abusers. Some clinical studies have shown that opium might be associated with alterations in the levels of total cholesterol, triglycerides, LDLc and HDLc, [3–5] whereas others have shown no significant difference in these parameters between individuals who are addicted and those who are not addicted to opium [6]. But standardized mortality ratios for CAD have been higher in opioid addicts as compared to general population. Although opioids have the protective effects on heart and play an important treatment role during ischemic event, the chronic usage of

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opioid may complicate influence of opioids, particularly when the consumption ways are different like inhalation [7]. Further, it have been shown that exogenous opioids tend to suppress the immune system and this negative modulation of immune cells depends on the opioid, its dose and the route of administration, possibly leading to low grade inflammation [8].

The effect of chronic abuse of heroin has been shown to cause oxidative stress in animal models, as well as in human studies [9]. Thus chronic opiate abuse may increase the hallmarks of cardiometabolic risk factors like dyslipidemia, inflammation and oxidative stress. However, there is a lack of data on the cardiometabolic profile of chronic opiate abusers from India, and a gap in the knowledge about the effect severity of opiate dependence on cardiometabolic profile. In the present study we aim to study the effect of chronic opiate abuse on the markers of cardiometabolic syndrome based on the severity of opiate abuse. Prevalence of cardiometabolic syndrome/metabolic syndrome was evaluated using NCEP ATP-III criteria [10].

Methods

In this hospital based, cross-sectional study 90 chronic opiate abusers (with or without associated smoking and non-smoking tobacco abuse) and 30 age matched controls were included. The study participants were categorized into four groups (I—healthy controls; II—pure opiate abusers; II—opiate and tobacco chewers; III—opiate and smokers). The opiate abusers were recruited prospectively from the de-addiction clinic of a tertiary care center in western India for a duration of 1 year i.e. from March 2015 to March 2016. The control group was recruited from the attendants of the substance abuse patients, who were having no complains of organic or functional diseases and who were not on any medication at the time of evaluation. The family history of the control subjects was taken and those with family history of cardiovascular disorders were excluded. An informed consent of the study protocol as approved by the institutional ethics committee was taken by all the participants prior to inclusion in the study.

Experimental

Inclusion Criteria

The study group from substance abuse were dependent on opiates (including pure opium, opium husk, and heroin) and or smoking and non-smoking tobacco. The study did not take into account the exact amount of opiate consumed,

but a minimum of 100 mg/day consumption was a criteria for selection of the subjects.

Exclusion Criteria

Exclusion criteria for the substance abuse persons were—age > 50 years, multiple substance abuse, diagnosed diabetics, hypertensive, CAD, patients taking rifampicin, ranitidine, nifedipene, levothyroxine to avoid cross reaction with urinary opiates analysis. The opiate abusers should have fulfilled the criteria of 100 mg/day opiate consumption for a minimum of 1 year abuse and dependence as per ICD 10 classification 1992 [11]. All opiate dependent patients should not have abstained for more than 24 h and the urine samples were analyzed for screening urinary opiate levels and those negative were excluded.

Anthropometric measurements of individuals wearing light clothing and no shoes were carried out. Weight was measured to the nearest 0.1 kg, and height was measured to the nearest 1 cm. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference (cm) was measured at the level of the iliac crest at the end of normal expiration. Waist circumference was measured to the nearest 0.5 cm. The subjects were screened for components of MS using modified ATP III criteria. Blood pressure was measured at rest in supine position three times and a mean was recorded. Biochemical analysis of fasting serum samples was performed on Beckman and Coulter AU 480 using the chemistry kits of Randox. The biochemical parameters analysed included fasting blood sugar (FBS; hexokinase method), lipid profile, serum insulin (chemiluminescence assay). IR in the participants was evaluated according to the homeostasis model assessment-insulin resistance (HOMA-IR) protocol [12]. Severity of opiate dependence was evaluated based on SODQ [13].

The study data was analyzed using SPSS 21 (Chicago, USA) software. The categorical data was expressed as mean and standard deviation. The difference between the groups was analyzed using one way analysis of variance (ANOVA), frequencies were used to determine the components of MS in different groups. Multiple linear regression was used to study the effect of independent variables on cardiometabolic risk factors.

Results

Most of the study participants were in the grade 3 of severity of opiate dependence and a large chunk of these belonged to the farming community, skilled workers (carpenters, goldsmiths, barbers, etc.) semi-skilled workers (masonry workers, labourers, etc.; Fig. 1). The prevalence

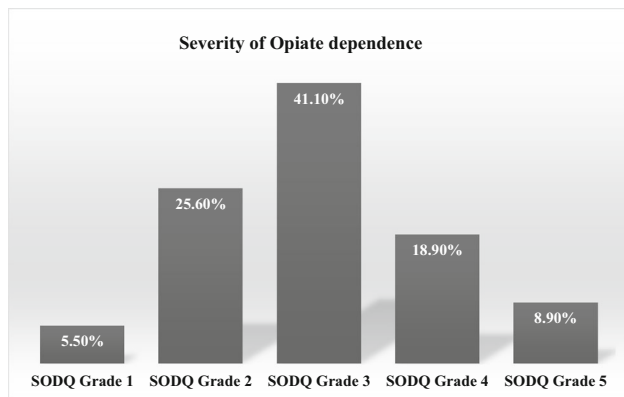


Fig. 1 Distribution of study participants based upon SODQ

of MS by the NCEP ATP III criteria was highest in opiate + smoke free tobacco users (43.3%), followed by opiate + smoking tobacco (33.33%), then pure opiate abusers (26.7%) and least in HCs (16.7%). One way ANOVA showed a significant difference across groups for BMI, WHR, TCH, TG, Hs-CRP and TAC (Table 1). Further multiple linear regression analysis conducted for pure opium abusers with opium dependency as dependent variable, showed dependency years were predicted independently by SBP, insulin, IR and advancing age (Tables 2) and Pearson's correlation analysis showed dependency to be significantly associated with HsCRP (Table 3). A multiple linear regression in SODQ grades 2 and 3 showed that TAC was independently predicted by

Hs-CRP ($p = 0.032$; $p = 0.042$) respectively (Tables 4, 5). Pearson's correlation analysis showed a significant association of TAC with serum insulin, IR and Hs-CRP in SODQ grade 2 and serum insulin and Hs-CRP in SODQ grade 3 (Tables 6, 7).

Discussion

The present study is the first of its kind in male, chronic opiate abusers with no associated co-morbidity. We observed that the cardio-metabolic profile of these subjects deteriorates with increasing severity of dependence due to increased oxidative stress and low grade chronic inflammation. The one way ANOVA showed significant difference between the groups ($p = 0.001$) and group II subjects had higher BMI and WHR as compared to the controls and opiate with co-dependence of tobacco (smoke and smokeless; Table 1). This probably is due to higher preferences for sweet and fatty foods as reported by Davis et al. [14] due to genotypic differences in the regulation of mu opioid receptors. Evidence from preclinical animal studies suggest that direct action of mu agonists at the nucleus accumbens shell, hypothalamus, and paraventricular nucleus is associated with development of sweet preference. Similarly, clinical literature demonstrates that chronic exposure to mu-opiate agonists leads to heightened taste preference for high-sugar foods [15]. The preference

Table 1 Basic cardio-metabolic profile of study groups and components of MS as per NCEP ATP III

	Group I (HC)	Group II (pure opiate)	Group III (opiate + tobacco chewers)	Group IV (opiate + smokers)	F and p values
BMI (kg/m ²)	22.66 (5.85)	23.59 (1.89)	21.31 (4.32)	21.84 (3.62)	1.68 (0.18)
WHR	0.89 (0.03)	0.9 (0.08)	0.85 (0.04)	0.9 (0.08)	4.44 (0.001)
SBP (mmHg)	121.27 (6.07)	125.97 (11.14)	128.20 (12.64)	128.60 (12.04)	2.91 (0.03)
DBP (mmHg)	81.87 (3.30)	83.13 (6.90)	81.80 (6.16)	83.57 (7.43)	0.63 (0.59)
FBS (mg/dl)	83.39 (15.59)	93.7 (9.47)	102.90 (15.25)	99 (16.49)	10.25 (0.0001)
TC (mg/dl)	180.77 (34.26)	174.1 (31.18)	169.83 (21.17)	170.4 (28.81)	0.88 (0.45)
TG (mg/dl)	119.33 (64.71)	138.87 (71.32)	113.9 (53.36)	115 (40.1)	1.18 (0.31)
HDL (mg/dl)	36.7 (8.02)	39.43 (5.17)	38.9 (8.12)	41.83 (40.10)	0.30 (0.80)
Insulin	7.57 (2.24)	8.21 (4.60)	8.98 (5.38)	12.25 (10.30)	3.22 (0.02)
HOMA-IR	0.99 (0.29)	1.12 (0.59)	1.23 (0.77)	1.6 (1.33)	2.95 (0.03)
Hs-CRP	0.2 (0.27)	0.28 (0.56)	0.38 (0.56)	0.28 (0.55)	0.65 (0.58)
TAC	1.70 (0.17)	1.79 (0.30)	1.82 (0.46)	1.59 (0.17)	3.57 (0.01)
NCEP criteria: frequency of MS (%) with all three components	16.7%	26.7%	33.33%	43.3%	–

Table 2 Multiple regression analysis of pure opium abusers for opiate dependence

	Unstandardized coefficients		Standardized coefficients	t	Sig.	95.0% CI for B	
	B	SE	Beta			Lower bound	Upper bound
Constant	9.422	35.401	Nil	.266	.799	– 77.20	96.04
WHR	– 11.342	10.149	– .142	– 1.118	.307	– 36.177	13.49
SBP	.452	.158	.745	2.865	.029	.066	0.83
DBP	.264	.444	.230	.594	.574	– .823	1.35
FBS	– .258	.178	– .538	– 1.451	.197	– .694	0.17
Insulin	31.289	11.466	22.271	2.729	.034	3.231	59.34
HOMA-IR	– 230.909	85.607	– 21.517	– 2.697	.036	– 440.38	– 21.43
TAC	– 1.670	3.834	– .066	– .435	.678	– 11.05	7.71
HsCRP	.226	2.370	.015	.095	.927	– 5.573	6.02
TCH	.016	.047	.079	.342	.744	– .099	0.13
TG	.021	.016	.224	1.318	.235	– .018	0.06
HDL	– .152	.188	– .100	– .809	.450	– .611	0.30
Age	.239	.094	.301	2.536	.044	.008	0.46

Model summary^{b,c}

Model	R		R ²	Adjusted R ²	SE of the estimate	Change statistics				
	Substance = opium (selected)	Substance ~ = opium (unselected)				R ² change	F change	Df1	Df2	Sig. F change
1	0.909 ^a	–	0.826	0.565	4.396	0.826	3.169	12	8	.050

^aPredictors: constant, hdl, sbp, homair, tg, fbs, whr, hscrp, tac, bmi, tch, dbp, insulin

^bUnless noted otherwise, statistics are based only on cases for which substance = opium

^cDependent variable: dependency

Table 3 Pearson’s correlation analysis of dependency years with cardiometabolic profile in pure opium abusers

Sig. (2-tailed)	Dependency	WHR	SBP	DBP	FBS	Insulin	Homa-IR	TAC	Hs CRP	TCH	TG	HDL	Age
Dependency	–												
WHR	.256	–											
SBP	.000	.280	–										
DBP	.000	.150	.000	–									
FBS	.368	.146	.406	.400	–								
Insulin	.399	.134	.379	.375	.261	–							
HOMA-IR	.391	.124	.383	.377	.192	.000	–						
TAC	.308	.180	.388	.249	.006	.044	.036	–					
HsCRP	.05	.334	.024	.002	.414	.347	.347	.327	–				
TCH	.272	.124	.182	.165	.270	.045	.041	.243	.158	–			
TG	.460	.358	.270	.299	.394	.370	.363	.115	.220	.000	–		
HDL	.245	.169	.498	.406	.154	.457	.469	.130	.161	.214	.445	–	
Age	.070	.011	.362	.222	.320	.402	.395	.359	.389	.308	.373	.153	–

for sugary foods resulting from opiate administration may lead to increased consumption of such foods, and possibly accumulation of excess body fat and weight gain. Current study also observed a significant difference ($p < 0.0001$) in

the FBS levels of the study groups in one way ANOVA, with highest FBS observed in the opiate + tobacco chewer group (Table 1). The increase in the FBS was linked with a significant increase in fasting insulin in the opiate abusers

Table 4 Multiple regression analysis for chronic opiate abusers in grade 2 SODQ with TAC as dependent variable

Model		Unstandardized coefficients		Standardized coefficients Beta	t	Sig.	95.0% confidence interval for B	
		B	SE				Lower bound	Upper bound
2	Constant	2.970	1.466	Nil	2.026	.070	– .296	6.236
	WHR	– .839	.616	– .334	– 1.362	.203	– 2.212	.534
	SBP	– .010	.007	– .444	– 1.479	.170	– .025	.005
	DBP	.007	.009	.210	.753	.469	– .013	.027
	Insulin	– .328	.233	– 13.382	– 1.411	.188	– .847	.190
	HOMA-IR	2.446	1.805	13.043	1.355	.205	– 1.576	6.467
	Hs-CRP	.212	.085	.539	2.492	.032	.022	.401
	TCH	.003	.003	.254	1.004	.339	– .004	.010
	TG	.000	.001	.044	.208	.839	– .002	.003
	HDL	– .006	.007	– .205	– .944	.367	– .021	.009
	FBS	– .007	.008	– .526	– .776	.456	– .025	.012
	Age	– .012	.009	– .443	– 1.434	.185	– .032	.007

^aDependent variable: tac

^bSelecting only cases for which sodq = 2.00

Table 5 Multiple regression analysis of chronic opiate abusers TAC with grade 3 SODQ

Model		Unstandardized coefficients		Standardized coefficients Beta	t	Sig.	95.0% confidence interval for B	
		B	SE				Lower bound	Upper bound
	Constant	– 29.374	43.901	Nil	– .669	.510	– 120.189	61.441
	WHR	– 12.733	14.491	– .147	– .879	.389	– 42.711	17.245
	SBP	.105	.109	.187	.965	.345	– .120	.330
	DBP	.059	.242	.047	.244	.810	– .442	.561
	Insulin	.349	1.146	.326	.304	.764	– 2.023	2.720
	HOMA-IR	– 8.378	8.875	– 1.054	– .944	.355	– 26.737	9.982
	Hs-CRP	5.985	2.783	.402	2.151	.042	.229	11.741
	TCH	.015	.056	.050	.265	.794	– .101	.131
	TG	.038	.025	.282	1.518	.143	– .014	.090
	HDL	– .082	.093	– .153	– .877	.390	– .275	.111
	FBS	.177	.224	.360	.792	.437	– .286	.641
	Age	– 2.036	2.161	– .155	– .942	.356	– 6.506	2.434

^aDependent variable: TAC

^bSelecting only cases for which sodq = 3.00

as compared to HCs (Table 1). Similar observations were made by Gozashti et al. [16] however they reported lower fasting insulin.

The relationship between the substance abuse and MS is complex with scarce literature. There is an increased risk of MS and diabetes in people with substance abuse and most studies have been performed in alcoholics and nicotine dependence. A study from northern India reports 29.3%

prevalence of MS in opiate dependence and included subjects with opiate dependence along with tobacco and smoking co-dependence [17]. However, current study reports for the first time opiate in combination with tobacco and smoking groups independently and observed significant difference in the FBS of these three groups, with highest in opiate with smoking (Table 1). The prevalence of MS in the current study was detected using ATP III

Table 6 Pearson's correlation analysis of TAC for opiate abusers with SODQ grade 2

Sig. (2-tailed) N = 23	TAC	WHR	SBP	DBP	Insulin	HOMA-IR	Hs-CRP	TCH	TG	HDL	FBS	Age
TAC	–											
WHR	.020	–										
SBP	.207	.409	–									
DBP	.455	.186	.001	–								
Insulin	.011	.008	.482	.108	–							
HOMA-IR	.011	.007	.451	.113	.000	–						
Hs-CRP	.008	.157	.455	.384	.164	.162	–					
TCH	.320	.162	.093	.397	.398	.353	.471	–				
TG	.305	.269	.452	.359	.355	.337	.278	.209	–			
HDL	.430	.313	.337	.453	.439	.433	.394	.067	.284	–		
FBS	.092	.149	.107	.431	.020	.009	.406	.118	.145	.423	–	
Age	.107	.048	.422	.131	.295	.332	.372	.234	.179	.056	.179	–

Table 7 Pearson's correlation analysis of TAC in chronic opiate abusers with grade 3 SODQ

Sig. (2-tailed) N = 37	TAC	WHR	SBP	DBP	Insulin	HOMA-IR	Hs-CRP	TCH	TG	HDL	FBS	Age
TAC	–											
WHR	.446	–										
SBP	.369	.446	–									
DBP	.371	.358	.004	–								
Insulin	.199	.498	.459	.224	–							
HOMA-IR	.235	.485	.484	.272	.000	–						
Hs-CRP	.281	.114	.264	.102	.398	.275	–					
TCH	.477	.071	.287	.349	.075	.075	.103	–				
TG	.424	.430	.173	.096	.216	.201	.186	.076	–			
HDL	.079	.264	.339	.495	.153	.112	.238	.047	.278	–		
FBS	.367	.432	.216	.212	.004	.001	.367	.090	.429	.147	–	
Age	.263	.048	.299	.184	.049	.099	.010	.433	.364	.437	.384	–

criteria with highest recorded in opiate with tobacco chewer, followed by opiate with smoking, then pure opiate group and least in HCs. The higher prevalence of MS in both opiate with (tobacco chewers or tobacco smokers) may be due to enhance inflammation as reported in earlier studies [18–21]. Further significantly higher serum insulin levels were observed in the opiate abusers as compared to the control group. This is in congruence with the observations that administration of naloxone (opioid antagonist) in obese subjects inhibited the responses of insulin and C-peptide to glucose administration and therefore possibly endogenous β -endorphins increase the responsiveness of pancreatic β cells. This may suggest that exogenous opioid administration may contribute to hyperinsulinemia [22].

Oxidative stress has been recently reported as key mechanism of developing IR [23]. Opioid drugs also

adversely affect the activity of antioxidant systems, as observed by decrease in the TAC in the blood of human heroin addicts when compared to the control groups [24]. In experimental mice exposed to heroin, there was a decrease in the activity of antioxidant enzymes in the brain such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) and administration of antioxidants alleviated the oxidative stress [25]. Multiple linear regression analysis of opiate abusers with MS showed that low grade chronic inflammation was predicted by increasing adiposity, BP, insulin, HOMA-IR, TC, HDL and LDL [26]. Inflammation is recognized as a major etiologic determinant of multiple disease states including myocardial infarction, stroke, diabetes, MS and individuals with elevated levels of the inflammatory biomarkers such as Hs-CRP are at increased risk of mortality and morbidity from

these conditions [27]. The current study also showed that oxidative stress significantly differed in the opiate abusers and was highest in group IV. This shows that opiate abuse along with smokeless tobacco dependence caused maximum oxidative stress. On adjusting for age, dependence years and basic biochemical profile, oxidative stress was independently predicted by the BMI and the serum insulin level of the opiate abusers. Further the correlation analysis of TAC showed that oxidative stress was negatively, significantly associated with dependence years, FBS, insulin and HOMA-IR. There are reports of heroin dependence being associated with increased IR in hepatitis C virus seronegative heroin abusers. Prolonged heroin abuse has been reported as associated with reduction of basal β -cell pancreatic function with decreased IR controlled for waist circumference, but still inducing significantly decreased basal insulin sensitivity [28].

Conclusion

We conclude that chronic opiate abuse is not benign for male abusers and there should be public awareness regarding the harmful effects of opiate abuse. Such subjects are a unique group with significant low grade inflammation and oxidative stress that drives for insulin resistance, even in the absence of co-morbidities like diabetes or hypertension. The consumption of opiates with smoking further adds to this risk. We recommend screening of opiate abuse patients for routine cardiometabolic profile.

Acknowledgements We acknowledge the support of technical staff at Department of Biochemistry, AIIMS Jodhpur and NGO Manklao de-addiction Centre for the constant support.

Funding This work was supported by All India Institute of Medical Sciences Jodhpur intramural funding Grant No AIIMS/RES9010/2014/0000038.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no potential conflict of interest.

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