

Evaluation of Antioxidant Status, High Sensitivity C-reactive Protein, and Insulin Resistance in Male Chronic Opiate Users Without Comorbidities

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ABSTRACT

Background: There is a paucity of data on frequency of metabolic syndrome (MS), insulin resistance (IR), and oxidative stress in Indian opiate users without comorbidities. **Objectives:** To determine the influence of opiate use on frequency of MS, homeostasis model assessment for IR (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), and oxidative stress in opiate-dependent male patients without comorbidities. **Methods:** Participants ($n = 120$) were grouped as controls (Group I), pure opiate dependents (Group II), opiate + tobacco dependents (Group III), and tobacco dependents (Group IV) with a minimum of 1-year dependence participated in the study. Participants were evaluated for anthropometric parameters, blood pressure (BP), fasting blood sugar, insulin, HOMA-IR, lipid profile, hs-CRP, and total antioxidant status (TAS). Frequency of MS was determined based on modified Adult Treatment Panel-III. The data were analyzed using one-way ANOVA, multiple regression by SPSS 21. **Results:** Frequency of MS in opiate dependents was higher than control. There was a significant difference in serum insulin, HOMA-IR, and TAS levels of the study groups. Multiple regression analysis showed dependence years, body mass index, waist-hip ratio, systolic blood pressure, diastolic blood pressure (DBP), HOMA-IR, and hs-CRP to be significant independent predictors of TAS in Group II and III patients with MS after adjusting for age and education years. TAS and DBP significantly predicted hs-CRP after adjusting for age and education years in Group II and III patients with MS. No such relation was seen in Group I and IV. **Conclusions:** Chronic opiate-dependent males without comorbidity are a unique group that shows low-grade inflammation, oxidative stress, and prevalence of MS predisposing them to future risk of cardiovascular diseases.

Key words: Antioxidant capacity, homeostasis model assessment-insulin resistance, high sensitivity C-reactive protein, metabolic syndrome, Opiate dependence

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INTRODUCTION

Opioid dependence poses significant public health risks arising from associated morbidity and mortality caused by cardiovascular diseases, accidents, infectious disease, and social ramifications of crime and unemployment, among other complications. Opium is the second most commonly abused substance after tobacco in developing countries of the Middle East region and in many Asian nations.^[1] In India, the number of opiate abusers is increasing every year with a great number residing in Western Rajasthan. There is an increased risk of metabolic syndrome (MS) and diabetes in people with substance use. The contributory factors for this increased risk could be nutritional deficiencies, increased cell damage, augmented excitotoxicity, reduced energy production, lowered antioxidant potential of the cells, etc.^[2,3] Most of the prevalence studies of diabetes in the substance use population have been conducted for alcohol and nicotine. There is a paucity of data on frequency of MS, insulin resistance (IR), and oxidative stress status in opiate-dependent persons from Indian population. The effects of opium use on diabetes mellitus have been controversial. There are reports of deteriorating glucose tolerance in type 2 diabetic patients with opiate dependence,^[4-6] and some observers reporting no change in the glycemic control of diabetics.^[7,8] However, there have been no studies, to the best of our knowledge, for studying the effect of chronic opioid addiction on serum insulin, IR, and total antioxidant capacity (TAS) among opiate use patients without any associated comorbidity. The aim of this study was to determine the potential influence of opiate use on frequency of MS, serum insulin, IR, and TAS in opiate-dependent male patients without any diagnosed comorbidity residing in Western Rajasthan.

METHODS

The study was conducted at the Department of Biochemistry and Department of Psychiatry of a tertiary care hospital. The study participants were opiate-dependent patients reporting to the psychiatry outpatient clinics, from April 2015 to February 2016 for de-addiction. The study was planned as case-control study. Age-matched controls were recruited from the relatives of the substance use patients residing under similar socioeconomic strata. The study included 30 controls (Group I), 30 chronic opiate users (Group II), 30 opiate and tobacco co-users (Group III), and 30 tobacco chewers (Group IV). The study protocol was approved by the Institutional Ethics Committee. Informed consent from all participants was taken. After enrollment into the study, a semi-structured pro-

forma was used to assess demographic and substance use details. The study group from substance use was dependent on opiates (including pure opium, opium husk, and heroin) and/or tobacco. The study did not take into account the exact amount of opiate consumed, but a minimum of 100 mg/day consumption was criteria for selection of the participants.

Exclusion criteria for the substance use persons of Group II, III, and IV were - age >50 years, diagnosed diabetics, hypertensive, coronary artery disease, and patients taking rifampicin, ranitidine, nifedipine, and levothyroxine to avoid cross-reaction with urinary opiates analysis. The opiate users should have fulfilled the criteria of 100 mg/day opiate consumption for a minimum of 1-year use and dependence as per ICD 10 classification 1992.^[9] All opiate-dependent patients should not have abstained for more than 24 h, and the urine samples were analyzed for screening urinary opiate levels.

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 participants were screened for components of MS using modified Adult Treatment Panel-III criteria.^[10] Blood pressure (BP) 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 analyzed included fasting blood sugar (FBS) (hexokinase method) and total antioxidant capacity (TAS) (2, 2'-Azino-di[3-ethylbenzthiazoline sulfonate] method). Fasting serum insulin was estimated using chemiluminescence (Liaison-Diasorin). IR in the participants was evaluated according to the homeostasis model assessment-IR (HOMA-IR) protocol.^[11]

Data are shown as means \pm standard deviation. All calculations and statistics were performed using IBM SPSS Statistics 21.0 software. The differences between groups were tested by one-way analysis of variance; $P < 0.05$ was considered statistically significant. Multiple linear regression analysis was done to adjust for the covariates, find out the strongest predictors of oxidative stress and high-sensitivity C-reactive protein (hs-CRP) in the study participants using enter method. Pearson's correlation analysis was done to find out any association between the studies variables.

RESULTS

Overall, the frequency of MS in substance use persons was higher as compared to the control population. Opiate-dependent patients had a higher frequency of MS than control participants and tobacco chewers had a higher frequency of MS than the controls and the opiate dependents [Table 1]. The difference between the groups and within the groups for the metabolic parameters using ANOVA was significant for Insulin, IR, and TAS [Table 2]. Multiple regression using enter method was performed for the substance use patients by SPSS 21. It showed that TAS of substance use patients with MS was significantly predicted by ($R^2 = 0.708$, $F = 3.65$, $P = 0.022$) their dependence years, systolic blood pressure (SBP), diastolic blood pressure (DBP), HOMA-IR, and hs-CRP levels [Table 3]. Further on running multiple regression for only Group II patients, there was a significant prediction of TAS by independent variables BMI, waist-hip ratio (WHR), SBP, DBP dependence years, FBS, WHR, hs-CRP, HOMA-IR ($R^2 = 0.61$, $F = 2.67$, $P = 0.05$) with DBP, and HOMA-IR being the most significant predictors on adjusting for age and education years. The Group III patients TAS was not significantly predicted by the independent variables BMI, WHR, SBP, DBP, dependence years, FBS, WHR, hs-CRP, and HOMA-IR ($R^2 = 0.53$, $F = 1.37$, $P = 0.27$) [Table 4]. Thus, suggesting that chronic opiate dependence causes variation in TAS, HOMA-IR, and hs-CRP of these patients with an increase in years of dependence, BMI, WHR, BP, FBS, and insulin. Group IV participants showed nonsignificant prediction of TAS and hs-CRP in age and

education year's adjusted models. Further correlation analysis after adjusting for age and dependence years, there was a significant association of TAS of Group II patients with WHR ($P = 0.043$), SBP ($P = 0.040$), DBP ($P = 0.013$), and FBS ($P = 0.020$). However, the Group III patients TAS showed a significant association with BMI ($P = 0.028$), SBP ($P = 0.037$) and hs-CRP ($P = 0.002$) [Tables 5 and 6].

DISCUSSION

This study for the first time reports the chronic opiate dependence causes oxidative stress, IR, and low-grade chronic inflammation with an increase in years of dependence, BMI, WHR, BP, FBS, and serum insulin. Opiate use may have multiple effects on endocrine and metabolic function of an individual. There is a long-standing belief of opiate use possibly causing an improvement in serum lipid profile and lowering the blood glucose concentrations. This study explored the effect of opiate use on cardiometabolic parameters of opiate-dependent male patients, without any chronic disorder. The frequency of MS in the pure opiate dependents was lower (26.7%) than those abusing opiate and tobacco (43.3%) which is higher than that reported in earlier studies from Northern India reported by^[12] Nebhinani *et al.*, 2013, but close to the Kerman Coronary Artery Disease Risk Factor Study from Iran in 2015 where a 39.6% frequency of MS in current opiate dependents was reported.^[13] Since the present study participants were based on strict exclusion criteria with no associated prediagnosed comorbidities, it tends to give a truer picture of frequency of MS in these participants. Higher obesity and WHR in the opiate

Table 1: Baseline characteristics one-way ANOVA of study population and frequency of metabolic syndrome as per Adult Treatment Panel III criteria

	Group I Healthy control (n=30)	Group II Pure opiate abusers (n=30)	Group III Opiate + tobacco chewers (n=30)	Group IV Tobacco chewers (n=30)	F	P
BMI (kg/m ²)	22.66 (5.85)	23.59 (1.89)	21.84 (3.62)	24.77 (4.06)	2.82	0.041
WHR	0.89 (0.03)	0.9 (0.08)	0.9 (0.08)	0.96 (0.09)	5.64	0.0012
SBP (mmHg)	121.27 (6.07)	125.97 (11.14)	128.03 (12.76)	139.83 (6.47)	20.54	0.0001
DBP (mmHg)	81.87 (3.30)	83.13 (6.90)	88.23 (4.79)	88.30 (3.78)	14.21	0.0001
Serum insulin (μIU/ml)	7.57 (2.24)	8.21 (4.60)	12.25 (10.30)	11.29 (4.79)	4.22	0.007
HOMA-IR	0.99 (0.29)	1.12 (0.59)	1.60 (1.33)	1.48 (0.64)	4.15	0.0189
FBS (mg/dl)	97.60 (15.59)	93.7 (9.47)	99 (16.49)	97.73 (16.16)	0.72	0.53
TG (mg/dl)	119.33 (64.71)	138.87 (71.32)	114.57 (40.05)	119.07 (56.69)	0.99	0.39
HDL (mg/dl)	36.7 (8.02)	39.43 (5.17)	41.83 (13.05)	36.07 (42.07)	0.41	0.74
TAC (mmol/L)	1.70 (0.17)	1.79 (0.30)	1.34 (0.09)	1.55 (0.64)	8.65	0.0001
hs-CRP (mg/L)	0.2 (0.27)	0.28 (0.56)	0.28 (0.55)	0.119 (0.15)	1.10	0.34
Frequency of MS (%) with all three components	16.7	26.7	43.3	50.0	-	-
Frequency of MS (%) with two components	20	30	20	30	-	-
Frequency of MS (%) with one components	40	26.66	26.66	3.33	-	-

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; FBS – Fasting blood sugar; TG – Triglyceride; HDL – High-density lipoprotein; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein; MS – Metabolic syndrome

Table 2: Multiple regression analysis of chronic opiate users (Group II and III) with metabolic syndrome after adjusting for age and education years

	Unstandardized coefficients		Standardized coefficients (β)	t	Significant
	B	SE			
For TAC*					
Constant	1.828	1.229		1.487	0.163
BMI	0.019	0.010	0.351	1.947	0.075
WHR	0.639	0.545	0.237	1.172	0.264
SBP	0.015	0.007	0.577	2.252	0.044
DBP	-0.036	0.013	-0.890	-2.707	0.019
FBS	0.002	0.003	0.147	0.718	0.487
HOMA-IR	-0.178	0.053	-0.834	-3.352	0.006
hs-CRP	0.525	0.222	0.526	2.368	0.036
Dependence years	-0.013	0.005	-0.427	-2.486	0.029
For hs-CRP*					
Constant	-3.498	1.024		-3.417	0.005
BMI	-0.003	0.012	-0.059	-0.254	0.804
WHR	0.379	0.845	0.140	0.448	0.662
SBP	-0.010	0.007	-0.388	-1.398	0.190
DBP	0.030	0.008	0.749	3.642	0.003
FBS	-0.001	0.003	-0.109	-0.494	0.631
HOMA-IR	0.055	0.060	-0.256	0.909	0.381
TAC	0.312	0.266	0.311	2.174	0.026
Dependence years	-0.002	0.008	-0.080	-0.320	0.755

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; FBS – Fasting blood sugar; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein; SE – Standard error

and tobacco users as compared to the controls and pure opiate abusers were observed, which is in concurrence with the reports seen in smokeless tobacco exposure effects in current users to cause higher markers of IR.^[14] One ANOVA showed a significant difference between SBP and DBP of the study groups [Table 1]. The SBP of the opiate-dependent patients (Group II and III) was significantly higher ($P = 0.04$) than that of controls and lower than that of tobacco chewers although nonsignificantly [Table 1]. This is in agreement with that of a report from Iran by^[15] Rahimi *et al.*, 2014, who observed significantly raised SBP in diabetic opium users as compared to healthy controls. The SBP was lower in the pure opiate abusers than patients using opiate and tobacco in combination. Further, the association of hs-CRP with DBP in pure opiate users agrees with the fact that hypertension indeed is a low-grade chronic inflammatory process. Increased BP may promote vascular inflammation by modulation of mechanical stimuli from pulsatile blood flow, and elevated BP is also known to promote the generation of reactive oxygen species^[16,17] as evident from a study where a significant correlation was observed between levels of CRP and mononuclear oxidative stress. The

Table 3: Multiple regression analysis of chronic opiate users (Group II) after adjusting for age and education years

	Unstandardized coefficients		Standardized coefficients (β)	t	Significant
	B	SE			
For TAC*					
Constant	6.359	1.729		3.678	0.002
BMI	0.008	0.012	0.162	0.721	0.482
WHR	0.653	0.860	0.188	0.759	0.459
SBP	0.007	0.011	0.265	0.654	0.522
DBP	-0.045	0.018	-1.030	-2.562	0.021
FBS	0.001	0.003	0.102	0.396	0.700
HOMA-IR	-0.204	0.066	-0.954	-3.080	0.010
hs-CRP	-0.011	0.008	-0.368	-1.350	0.204
Dependence years	0.510	0.314	0.512	1.624	0.133
For hs-CRP*					
Constant	3.768	3.031		1.243	0.230
BMI	0.016	0.024	0.163	0.654	0.522
WHR	-0.247	1.733	-0.038	-0.143	0.888
SBP	0.034	0.024	0.671	1.431	0.170
DBP	-0.096	0.042	-1.185	-2.311	0.033
FBS	0.011	0.008	0.309	1.433	0.169
HOMA-IR	-1.305	0.602	-1.381	-2.167	0.044
TAC	0.24	0.43	0.13	0.55	0.58
Dependence years	-0.023	0.025	-0.257	-0.935	0.362

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; FBS – Fasting blood sugar; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein; SE – Standard error

current study also showed a significant association of hs-CRP with TAS in opiate + tobacco users, showing coexistence of low-grade chronic inflammation and oxidative stress in these patients probably adding up to their IR and hypertension [Table 6].

The patients with substance use showed higher serum insulin, HOMA-IR than the age-matched control population. The one-way ANOVA showed a significant difference between the groups for serum insulin and HOMA-IR [Table 1]. In the opiate use patients, islet cells responsible for the production of insulin do not respond in an appropriate manner to the glucose signals. This state is similar to the state of diabetes as evidenced by increased concentration of hemoglobin A1c (HbA1c) and reduction of acute insulin to glucose given intravenously in some studies.^[18] Further, the administration of naloxone (opioid antagonist) in obese patients inhibited the responses of insulin and C-peptide to glucose administration. This suggests that endogenous β-endorphins increase the responsiveness of pancreatic β cells. This may suggest that exogenous opioid administration may contribute to hyperinsulinemia, and prolonged use has been

reported to induce significantly reduced basal insulin sensitivity.^[3,19]

IR has been shown to induce oxidative stress by generating excessive superoxide anion or H₂O₂ and decreasing catalase synthesis. This is part of a feed-forward mechanism that results in chronic conditions of oxidative stress and inflammation, leading to modulation of vascular endothelial function,

smooth muscle contractility, and organ function.^[20] One way ANOVA also showed a significant difference between the hs-CRP levels of Group I, II, and III [Table 1]. This signifies the effect of opiate and tobacco use on inflammatory status and suggests underlying immune stimulation that may play a role in the development of MS and future cardiovascular risk.^[21]

Table 4: Multiple regression analysis of chronic opiate users (Group III) after adjusting for age and education years

	Unstandardized coefficients		Standardized coefficients	t	Significant
	B	SE	β		
For TAC*					
Constant	0.934	0.300		3.119	0.005
BMI	0.008	0.005	0.294	1.452	0.161
WHR	-0.152	0.226	-0.129	-0.674	0.508
SBP	0.003	0.002	0.378	1.581	0.129
DBP	0.000	0.003	-0.011	-0.041	0.967
FBS	0.001	0.001	0.109	0.535	0.598
HOMA-IR	-0.006	0.015	-0.085	-0.394	0.697
hs-CRP	-0.072	0.030	-0.421	-2.413	0.025
Dependence years	-0.002	0.002	-0.147	-0.781	0.443
For hs-CRP					
Constant	7.766	3.567		2.178	0.042
Age	0.007	0.013	0.127	0.571	0.574
BMI	-0.021	0.034	-0.141	-0.640	0.530
WHR	-0.934	1.783	-0.135	-0.524	0.606
SBP	-0.008	0.014	-0.163	-0.546	0.591
DBP	0.018	0.021	0.243	0.854	0.404
FBS	-0.023	0.022	-0.682	-1.040	0.312
Insulin	-0.755	0.539	-14.052	-1.401	0.177
HOMA-IR	6.064	4.321	14.578	1.403	0.177
Dependence years	-0.005	0.018	-0.073	-0.258	0.799

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; FBS – Fasting blood sugar; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein; SE – Standard error

The present study reports of a significant difference in the antioxidant status of the Group II, III, and IV, with the least levels in Group III (*P* = 0.0001). This report matches the findings that opioid drugs impair the activity of antioxidant systems, as demonstrated by the decrease in TAS found in blood of human heroin addicts, when compared to detoxification and control groups,^[16] and a reduced activities of superoxide dismutase, catalase, and glutathione peroxidase and in the ratio of GSH to GSSG were found in the brains of heroin-exposed mice^[22,23] and in C6 cells after morphine treatment.^[24] Besides, the additional finding in the current study is the greater drop in TAS of opiate users, if they are concomitantly exposed to tobacco than pure opiate alone.

This study for the first time reports the correlation of serum TAS with SBP, DBP, WHR, and FBS in Group II patients, suggesting the drop in TAS to be associated with hypertension and raised risk of MS by affecting WHR in Indian chronic opiate using patients. Further, the association of TAS with hs-CRP in Group III patients suggests a decrease in TAS possibly leads to low-grade inflammation in this group.

The limitation of the study is the small sample size per group which prevents the generalization of these findings to a larger population. Larger prospective study will help in confirming the study data for a generalized opiate-dependent population. The study included only male patients as the females of the area do not report to de-addiction centers in this part of India as it is a

Table 5: Correlation analysis of Group II patients after adjusting for age and education years

Significant (two-tailed)	TAC	BMI	WHR	SBP	DBP	FBS	HOMA-IR	hs-CRP	Dependence years
TAC									
BMI	0.099								
WHR	0.043	0.014							
SBP	0.040	0.174	0.438						
DBP	0.013	0.127	0.465	0					
FBS	0.020	0.073	0.308	0.382	0.471				
HOMA-IR	0.090	0.482	0.121	0.488	0.444	0.030			
hs-CRP	0.214	0.226	0.329	0.058	0.039	0.240	0.276		
Dependence years	0.277	0.167	0.166	0.001	0.013	0.477	0.448	0.027	

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; FBS – Fasting blood sugar; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein

Table 6: Correlation analysis of Group III patients after adjusting for age and education years

Significant (two-tailed)	TAC	BMI	WHR	SBP	DBP	HOMA-IR	hs-CRP	Dependence years
TAC								
BMI	0.028							
WHR	0.273	0.083						
SBP	0.037	0.419	0.164					
DBP	0.072	0.116	0.135	0				
HOMA-IR	0.459	0.116	0.005	0.434	0.274			
hs-CRP	0.002	0.104	0.451	0.463	0.338	0.498		
Dependence years	0.324	0.296	0.348	0.099	0.033	0.028	0.159	

BMI – Body mass index; WHR – Waist-hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HOMA-IR – Homeostasis model assessment for insulin resistance; TAC – Total antioxidant capacity; hs-CRP – High-sensitivity C-reactive protein

patriarchal society that is highly conservative although opiate use is a part of the social fabric.

CONCLUSIONS

We conclude that the opiate dependent-male subjects are a unique group which even in the absence of any comorbidities show low-grade inflammation, reduced TAS, and prevalence of MS which puts them at future risk of cardiovascular diseases and should be evaluated independently for it.

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Conflicts of interest

There are no conflicts of interest.

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