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Prevalence & correlates of metabolic syndrome in alcohol & opioid dependent inpatients

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***Background & objectives*: The research on the association of metabolic syndrome (MS) and substance abuse is scanty. The present research aimed to study the prevalence and correlates of MS among the inpatients at a Drug De-addiction Centre in north India.**

***Methods*: Consecutive male subjects (N=110) admitted to a drug de-addiction centre during July to December 2009 with a primary diagnosis of alcohol or opioid dependence were evaluated for the presence of MS as per the International Diabetes Federation (IDF) criteria.**

***Results*: The prevalence of MS was 24.6 and 29.3 per cent in alcohol and opioid dependent groups, respectively. MS showed a significant association with the age and body mass index (BMI) in the opioid dependent group. Co-morbid tobacco use was not associated with MS in either group.**

***Interpretation & conclusions*: The prevalence of MS in our sample of alcohol and opioid dependent male inpatients was greater than the prevalence of MS in general population, however it was comparable to that reported in physical and other psychiatric disorder populations. Even though the absence of any comparative study limits the generalizability of our findings, results indicate towards a need for screening of the patients with substance dependence especially for those aged above 30 years and/or having a high BMI for MS.**

Key words Metabolic syndrome - prevalence - substance dependence

First described[1] by Gerald Reaven in 1988, the 'syndrome X' has also been named as 'insulin resistance syndrome', and 'CHAOS' (a mnemonic for Coronary artery disease, Hypertension, Adult onset diabetes, Obesity and Stroke). However, metabolic syndrome (MS) has become the most useful and widely accepted term for this cluster of metabolically related cardiovascular risk factors which also predict a high risk of developing diabetes (if not already present). Its pathophysiology remains obscure but has been hypothesized to involve insulin resistance and a pro-inflammatory state[2,3]. The Third National Health and Nutrition Examination Survey in the United States reported the prevalence of MS at 24 per cent in healthy adults and found the cardiovascular and all-cause mortalities to be increased in men and risk of coronary disease increased in women[4]. The men with MS have been reported to be 2-4 times more likely to die of any

cause than those without MS, even after adjustment for conventional risk factors[5]. Thus, the potential risks of MS, and its public health importance are immense.

The criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP III)[6] with revision in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (updated ATP III)[7], and the International Diabetes Federation (IDF)[8] are widely accepted as these provide a differential profile for populations of Asian origin. These definitions lay emphasis on abdominal obesity (abdominal circumference of >90 and >80 cm respectively for men and women of Asian origin, and of 102 and 88 cm respectively for non-Asians). The other criteria are triglyceride (TG) levels >150 mg/dl, high density lipoproteins (HDL) <40 and 50 mg/dl for men and women respectively, a systolic blood pressure (SBP) >130 mm of mercury (Hg) or a diastolic blood pressure (DBP) >85 mm of Hg and fasting plasma glucose (FPG) levels >100 mg/dl. The advantages of being easily measurable and not requiring specialized investigations have made the IDF and updated ATP definitions more acceptable compared to the WHO criteria[9] proposed earlier.

In relation to substance use the research has mostly focused on the association between MS and alcohol. Some studies have reported moderate alcohol use to be associated with a lower prevalence of metabolic syndrome[10,11]. Under the 1998 Korean National Health and Nutrition Examination Survey covering 7962 adults (3597 men, 4365 women), the prevalence of the MS has been reported as 20.8 per cent in men and 26.9 per cent in women[12]. The adjusted odds ratio for the MS in the group with daily consumption of 1-14.9 g alcohol was 0.71 (95% CI: 0.53, 0.95) in men and 0.80 (95% CI: 0.65, 0.98) in women. Alcohol consumption had a significant inverse relation with the odds ratio for low HDL cholesterol in all alcohol subgroups. Heavy alcohol consumption (≥30 g/day) was associated with significantly higher odds ratios for high blood pressure and high TG in men and high FPG and high TG in women. The analysis of the data from the Third National Health and Nutrition Examination Survey, USA, found the prevalence of the MS to be higher in women (22.7%) compared to men (21.9%)[13], as also that the current drinkers had a lower adjusted prevalence of MS than subjects not currently drinking [OR 0.57 (95% CI 0.45- 0.72)]. From Portugal, a prevalence of 3.5-42.3 per cent was reported for MS, with no significant association with alcohol intake[14].

Among the studies that specifically looked into the prevalence of MS in alcohol dependent (AD) subjects, a study from Brazil reported prevalence of MS to be 5.1 per cent in alcohol dependent (AD) psychiatric inpatients[15]. Another study from USA found 22 per cent of the subjects meeting the criteria for MS in a sample of alcohol and nicotine dependent adults[16]. Finally, a recent study from Germany estimated the prevalence of MS to be 30.6 and 17 per cent in AD men and women, respectively[17].

There is no study available reporting on the prevalence of MS in substance dependent population from India, as also the prevalence of MS in opioid dependent (OD) subjects from anywhere in the world. Thus, the present investigation aimed to study the prevalence and selected demographic and clinical correlates of MS in the AD and OD subjects among the consecutive inpatients at a Drug De-addiction Centre in north India.

Material & Methods

The study was conducted at the Drug De-addiction and Treatment Center (DDTC) of the department of Psychiatry at the multispecialty general hospital of Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The sample included of consecutive admissions between July 15 and December 15, 2009. The subjects were those hospitalized for detoxification followed by de-addiction (consisting of various psychosocial managements in all cases and prophylactic medications against relapse such as disulfiram or naltrexone in some cases). The data for MS were collected at a time usually 10-15 days after the ward admission when detoxification regime was over, and the patients were no longer in withdrawal as assessed by structured withdrawal proforma routinely used for our inpatients and before or just at the start of any prophylactic medication, if at all. The subjects admitted more than once were assessed only the first time.

Ethical clearance for the study protocol was obtained from the Institute Ethics Committee.

The diagnosis of substance dependence was made as per the ICD-10[18]. The subjects dependent only on substances other than alcohol or opioids or on both were excluded to bring homogeneity to the study population and to allow the comparison of MS between alcohol and opioid dependent subjects. For the assessment of MS the IDF criteria[8] were used.

Written informed consent was obtained from the patients (or attendants, when the patients were not competent to give consent). As a part of the routine admission procedure height, weight and blood pressure were recorded and biochemical parameters obtained; additionally waist circumference was recorded.

The socio-demographic and clinical data were obtained from the patients and reliable attendants through the clinical interview. The primary ICD diagnosis recorded for the study was the one coded at the time of discharge from the wards. For the ease of analysis, the diagnoses were divided under two broad headings-alcohol group (subjects dependent on alcohol, with or without dependence on tobacco and substances other than opioids) and opioid group (subjects dependent on opioids, with or without dependence on tobacco and substances other than alcohol).

Physical activity of the subjects was assessed by a modified physical activity subscale of the Health Promoting Lifestyle Profile scale (HPLP II)[19]. Activities such as sports, cycling, walking, running and swimming were taken into account. Subjects spending >30 min/per day in those activities were considered to have an active lifestyle.Waist circumference was measured in centimeters (cm) using a measuring tape in the horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest; measurement being recorded at the end of normal expiration. Along with the waist size, weight in kilogram (kg) using a common bathroom scale and height in cm using a calibrated scale were recorded at admission. The body mass index (BMI kg/m^2) was calculated from the weight and height. The BP was defined as the average systolic and diastolic BP (SBP and DBP) in mm of Hg recorded during the patients' ward stay. The triglyceride (TG), high density lipoprotein (HDL), fasting plasma glucose (FPG) and low density lipoprotein (LDL) levels (mg/dl) were measured at the routine biochemistry laboratory of the hospital using fasting venous blood samples and a random access autoanalyser, model modular-P from Roche Diagnostics, Germany.

Subjects met the IDF criteria[8] of MS if they had the waist circumference of > 90 cm for males and ≥80 cm for females, along with 2 or more of the following criteria: elevated TG >150 mg/dl, decreased HDL <40 mg/dl for males and <50 mg/dl for females or receiving treatment for dyslipidaemia; elevated BP >130 mm Hg systolic or >85 mm Hg diastolic or receiving treatment for hypertension; and elevated FPG >100 mg/dl or receiving treatment for the same.

Regarding sample size calculation, we consulted the only three studies available for prevalence of MS in AD subjects[15-17]. Because the prevalence figures varied widely, from 5 to 31 per cent, we estimated the prevalence to a mean figure of 17 per cent. Further, to capture the wide range of reported prevalence, the precision value (d) was set to 10 per cent (so as to yield a 95% confidence interval of 7 - 27%)[20]. With this, using a standard statistical software[21], the required sample size was 55 (range 45-65). Because there was no previous study on OD subjects, we empirically followed the same calculation as for alcohol. Accordingly, we attempted to recruit a sample size of 45-65 for each of the two groups.

Data analysis: The data were analyzed using SPSS version 15.0 for Windows (Chicago, Illinois, USA). For the continuous variables descriptive statistics were used and comparisons done with the Independent samples t-test, from which mean and standard deviation (SD) with 95 per cent confidence intervals were computed. For the categorical variables frequencies and percentages (%) were computed with the Pearson Chi-squared test with Yates' correction or Fisher's exact test. Binary logistic regression procedure was followed to estimate the strength of association between the independent variables and the presence of metabolic syndrome. A model for the regression analysis was made by entering each independent variable except those comprising the criteria for MS singly into the binary logistic regression and chosen for inclusion into the model if the P<0.1 for that independent variable. We did not try to categorize the continuous predictor variables into ordinal or other categories. Odds ratio (OR) with 95 per cent confidence interval (CI) were computed for the model derived as per the above scheme in the whole study population, and for the patients in the broad diagnostic groups of psychoses and affective disorders. For further sub-analysis, patients were divided into 2 groups: with BMI <25 and others. These two groups were entered into the binary logistic regression to find the odds ratio of having MS if the BMI of the patient was >25 kg/m^2.

Results

Of the 116 men admitted to the ward during the study period, six were excluded from the analysis as they were dependent on substances other than alcohol

or opioids (*e.g.* cannabis, inhalants). Therefore, the final sample consisted of 110 men.

Of the 110 men included in the study, the profile of a typical subject was: educated for >10 yr (80.9%); married (80%); earning > 6000 ₹ per month (60%); urban (59.1%); nuclear family (58.2%); retired, student or unemployed (31.8%), clerical, shop-owner or businessmen (30%), or farmer or semi-skilled worker (21.8%). The mean age was 37.43±0.89 yr for current age, 21.53±.83 yr for onset of substance use, and 27.17±7.02 yr for onset of substance dependence. The mean duration of dependence was 10.58 ±9.70 yr.

The alcohol group (n=69) substance use profile was: alcohol only (n=22), alcohol+tobacco (n=34) and alcohol+other non-opioids (mostly benzodiazepines) (n=13). The opioid group (41) profile was: opioids only (n=8), opioid+tobacco (n=23), opioid+others **(**mostly benzodiazepines**)** (n=10). Majority (49.1%) had a dependent use of >2 substances over lifetime.

Majority of the subjects did not have any physical (67.3%) or psychiatric (82.7%) co-morbidity (Table I). The commonest physical co-morbidities were seizure disorder and liver disease (n=8, each), hypertension (n=6) and diabetes mellitus (n=5). The commonest psychiatric co-morbidity was psychotic illness (n=7). Majority (82.7%) of the subjects were not receiving any psychotropic medication and/or medication for substance dependence. Past history of hospitalization related to substance dependence was present in 30 per cent of the subjects. History of intravenous opioids and sexual intercourse with commercial sex workers was present in 9 (8.2%) and 8 (7.3%) subjects, respectively. HIV and HCV were positive in 1 subject each in the opioid group.

Majority of the subjects had an active lifestyle (57.3%). The profile of health promoting activities was: walking (n=60), sports (n=12), cycling (n=11), running (n=5), and swimming (n=3). The mean daily duration of such activities was 51.77+59.88 min.

The prevalence of the MS (as per IDF criteria) was 24.6 per cent (17/69) for alcohol group, and 29.3 per cent (12/41) for opioid group; the difference in prevalence between the two groups was not significant. No significant difference in the prevalence of MS was noted in tobacco +ve and tobacco –ve subjects, both for alcohol and for opioid groups.

Table I. Clinical profile of the sample (N=110)

Clinical variables	N(%)
A. Comorbid medical diagnoses:	
Nil	74 (67.3)
Seizure disorder	8 (7.3)
Liver disease	8 (7.3)
Hypertension	6 (5.4)
Diabetes mellitus	5 (4.5)
Others (included neuropathy, ocular problem, cardiopulmonary insufficiency, gout & sexual dysfunction)	9 (8.1)
B. Co-morbid psychiatric diagnoses:	
Nil	91 (82.7)
Psychotic disorders	7 (6.4)
Affective disorders	6 (5.4)
Anxiety disorders	5 (4.5)
Obsessive compulsive disorder	1 (0.9)
C. Psychotropic medications received by the subjects:	
Nil	91 (82.7)
Second generation antipsychotics (SGAs)	8 (7.3)
Disulfiram	5 (4.5)
Antidepressants (Serotonin norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitor, *etc.*)	5 (4.5)
Naltrexone	4 (3.6)
Sodium valproate	4 (3.6)
Benzodiazepines	1 (0.9)

Subjects with MS had higher mean age, waist circumference, total TG, SBP and DBP, weight and BMI, TG level >150 mg/dl, and lower HDL. FPG, height and lifestyle did not differ for the presence or absence of the MS (Table II).

Table III presents the results of the binary logistic regression for the two diagnostic groups. Age and BMI were positively and significantly correlated with presence of MS for the opioid group. In other words, with each unit increase in age and BMI, the likelihood of the patient having MS increased in a statistically significant manner. For alcohol group, the independent variables did not reach significance but the ORs suggest an increasing likelihood of MS with increasing age, body weight and BMI.

Discussion

The prevalence figures of MS in AD subjects vary widely from 5 to 31 per cent[15-17]. A prevalence of MS of 24.6 per cent in alcohol group in our study seems to corroborate the findings from earlier studies. Across

Table II. Metabolic syndrome and its relationship with clinical variables

	Total (n=110)	MS as per IDF		*P* value
		Present N (%)	Absent N (%)	
A. Categorical variables:				
Elevated triglyceride (TG) (as per IDF)	61	25 (41)	36 (59)	<0.001*
Sedentary	47	14 (29.8)	33 (70.2)	0.853*
Active	63	15 (23.8)	48 (76.2)	
B. Continuous variables:	Mean ±SD			
Age (yr)	37.43 ± 10.89	41.72 ± 11.03	35.89 ± 10.49	0.013
Age at first substance use (yr)	21.53 ± 4.83	21.55 ± 4.34	21.52 ± 5.02	0.975
Age at substance dependence (yr)	27.17 ± 7.02	28.28 ± 6.69	26.78 ± 7.14	0.327
Total years of dependence	10.58 ± 9.70	13.03 ± 9.67	9.7 ± 9.62	0.113
Duration of activity (min)	51.77 ± 59.88	47.24 ± 60.02	53.39 ± 60.12	0.637
Waist circumference (cm)	87.82 ± 9.92	97.86 ± 7.65	84.22 ± 7.99	<0.001
Total TG (mg/dl)	189.19 ± 146.11	281.55 ± 227.12	156.12 ± 82.67	<0.001
High density lipids (mg/dl)	55.34 ± 24.74	44.19 ± 16.14	59.32 ± 26.10	0.004
Fasting blood sugar (mg/dl)	103.51 ± 47.97	102.74 ± 31.90	103.79 ± 52.71	0.920
Systolic blood pressure (mmHg)	119.05 ± 12.62	127.86 ± 12.64	115.90 ± 11.08	<0.001
Diastolic blood pressure (mmHg)	79.45 ± 10.25	84.59 ± 11.21	77.61 ± 9.28	0.001
Weight (kg)	65.95 ± 13.95	77.79 ± 17.07	61.72 ± 9.67	<0.001
Body mass index (kg/m^2)	22.68 ± 4.07	26.52 ± 4.19	21.31 ± 3.03	<0.001
Height (m)	1.70 ± 0.07	1.71± 0.09	1.70 ± 0.06	0.700

IDF, International Diabetes Federation; *As per Pearson Chi-square, other results as per Means procedure

Table III. Binary logistic regression analysis

	Variable	Coefficient B	Standard Error (SE)	Odds Ratio	95% CI
A.	*Binary logistic regression analysis for Alcohol group (N=69)*:				
	Age	0.034	0.041	1.035	0.954-1.122
	Body weight	0.022	0.071	1.022	0.891-1.174
	BMI	0.412	0.255	1.509	0.916-2.487
	Constant	-13.788	3.520		
B.	*Binary logistic regression analysis for Opioid group (N=41)*:				
	Age	0.124	0.052	1.132	1.023-1.253
	Body weight	-0.058	0.077	0.944	0.812-1.098
	BMI	0.620	0.300	1.859	1.033-3.345
	Constant	-15.931	4.731		

Association significant when *P*<0.05

our AD and OD groups the prevalence of MS was similarly high. We could not find any study reporting on the prevalence of MS in OD subjects. Therefore, the prevalence of MS of 29.3 per cent for the opioid group in the index study can serve as a reference for future studies. Moderate alcohol use has been reported to be associated with a lower prevalence of MS[10,11]. However, it was difficult to compare with moderate drinkers because all alcohol users in our study were alcohol dependent. In the study by Kahl *et al*[17] tobacco use (pack-years) did not emerge as a significant independent predictor of MS in AD subjects. Similarly in our study tobacco use was not found to significantly influence the prevalence of MS in both alcohol and opioid groups.

Among the general population the studies from India have reported a wide range of prevalence rates for MS. These include the lowest rate of 4.7 per cent among adolescents at Chandigarh[22] using ATP-III

criteria, 13 per cent among adults in Jaipur[23] using ATP III, 18.4 per cent in men and 30.9 per cent in women among randomly selected adults in Jaipur[24] using the ATP III criteria, 25.8 per cent in adults in Chennai (urban and rural)[25] using IDF criteria, 41 per cent in Chennai[26] using the modified ATP III criteria and 47.4 per cent among adults at Chandigarh[27] using the IDF criteria. Regarding MS in schizophrenia and mood disorders the prevalence rates of 36-60 per cent have been reported from the West[28-30]. From our centre[31] the prevalence of 37.8 per cent has been reported among the psychiatric inpatients using IDF criteria. In contrast, in physical disorders such as type 2 diabetes mellitus and acute myocardial infarction the prevalence of MS was reported to be 86 and 26.19 per cent respectively using two different criteria[32,33].

In our subjects 4 of the 5 components of MS (waist circumference, TG levels, HDL, elevated blood pressure) significantly differentiated those with MS from those without; the only exception was FPG. Moreover, 44.5 per cent of subjects with waist circumferences above the cut-off point fulfilled the criteria of MS as per IDF. Those with a BMI of >25 kg/m^2 (23.6% of our subjects) were significantly more likely to have MS than those without. Considering these facts, it appears that the measurement of height, weight and waist circumference should form a part of initial assessment of patients seeking treatment in a drug de-addiction centre especially for those aged >30 yr.

Our subjects with MS had higher mean age and total years of dependence on the substance, though not significantly different. This trend was consistent with the reported contribution of increasing age to the number of MS diagnostic components[34], indicating that factors associated with ageing and deleterious effects of substances consumed over a prolonged period of time may be contributory to MS. In support of this premise, lower prevalence of MS has been reported to be associated with moderate to vigorous physical activity by studies that used both objective and subjective measures[34,35]. However, to the contrary, a study on community dwelling elderly men and women in south Brazil[36] found no significant association between MS and level of physical activity as per International Physical Activity Questionnaire. In our study also the type of lifestyle had no impact on the prevalence of MS. Our finding of BMI having a significant correlation with the presence of MS is supported by another study from the same centre but on psychiatric inpatients[31].

Our study had the following highlights: consecutive sampling; patients were included in the study after 10-15 days of admission when acute withdrawal symptoms were remitted because assessment under the influence of alcohol/opioid or during withdrawal distorts the findings systematically through their effect on autonomic nervous system and glucose metabolism; perhaps the first study from India to find out the prevalence of MS in substance users.

Our study has limitations. The sample, taken from the inpatient setting of a tertiary care hospital, could not be considered to be truly representative of the community. The admission policy of our institute preventing the inclusion of women, limits the generalization of the findings. The cross-sectional nature of the study meant that the causal pathways of MS could not be inferred. The lack of genetically related control group and non-consideration of dietary habits limit the conclusions on causal links. Because of our admission policy substance dependent patients with current psychiatric co-morbidity requiring active intervention did not figure in our sample which limits its generalizability to 'real world' population in whom psychiatric co-morbidity is the rule rather than the exception. Moreover, a few patients were receiving psychotropic medications which to some extent might have influenced the findings.

Despite these limitations our study opens an area that deserves further research in India with larger samples, prospective and longitudinal designs, and focus on the prevalence as well as the correlates of MS in substance using populations.

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