

Association of metabolic syndrome with schizophrenia

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ABSTRACT

Background: Metabolic syndrome (MetS) is associated with mental illnesses. It is a major predictor of mortality and morbidity in patients of such mental illnesses. This study was undertaken to study the association of MetS and schizophrenia. **Objectives:** To study the association of MetS in patients of schizophrenia. **Materials and Methods:** Adult schizophrenic patients diagnosed as per Diagnostic and Statistical Manual -IV Third Revision criteria visiting the psychiatric Out Patient Day during the study period were evaluated for prevalence of MetS as per the criteria of the international diabetes federation. Fifty patients of schizophrenia with age- and sex-matched 50 controls were enrolled for the study. **Results:** MetS was found to be 28% in patient group and 12% in control group ($P < 0.05$). Fourteen patients were found to have MetS out of 38 patients who were on antipsychotics for >6 months. All the 14 patients having MetS were taking second-generation antipsychotics (SGAs) ($P < 0.05$). **Conclusion:** The study showed a higher prevalence of MetS in schizophrenia than in general population. MetS was present only in patients taking SGAs and prevalence of MetS had a positive correlation with duration of treatment. The study points toward urgent need for consultation – liaisoning between Diabetologist and Psychiatrists.

Key words: Metabolic syndrome, schizophrenia, second-generation antipsychotics

INTRODUCTION

Psychiatric disorders are associated with increased medical morbidity and mortality that are largely due to treatable medical conditions such as cardiovascular disease (CVD), diabetes, respiratory, and infectious diseases. Recognition and management of medical morbidity in patients with psychiatric illnesses are difficult due to barriers related to the patient, the illness, the attitudes of medical practitioners, and the structure of healthcare delivery services.^[1]

During last several years there has been growing interest

in metabolic abnormalities in schizophrenia. These disturbances are highly co-incident and metabolic syndrome (MetS), which is seen in around 3-4% in general population has an incidence of around 10% in schizophrenic patients. MetS is a cluster of risk factor, for CVD comprising of central obesity, dyslipidemia, hypertension, and elevated fasting plasma glucose levels.^[2]

Schizophrenic patients with the MetS have higher rates of coronary heart disease, myocardial infarction, and stroke than the same patients with any one of the components of hypertension, insulin-resistance, dyslipidemia, or obesity.^[3]

The risk of these medical co-morbidities is further increased by the use of psychotropic medications that are used for the treatment of such patients. The risk may be greater with some second-generation antipsychotic (SGA) agents.^[4]

The SGA medications have been associated with weight gain, diabetes, dyslipidemia, insulin resistance, and the MetS.^[5] There are number of studies which have found that the risk of MetS is greater in those receiving psychotropic

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medications as compared to the general population. Studies in this context are lacking in India. Thus, in this study, prevalence of MetS in patients of schizophrenia was assessed. This is likely to help and have a bearing on choosing appropriate psychotropic medications for these patients and need for multidisciplinary approach for holistic healthcare.

MATERIALS AND METHODS

Case selection

- Known cases of schizophrenia, according to DSM-IV criteria, are selected from the patients who attended psychiatric OPD in our hospital
- Age: 18-50 years
- Informed consent was obtained in written and the institutional ethical committee's permission was obtained.

Control selection

- The control group comprised of age-and sex-matched volunteers.

Exclusion criteria

- Presence of diagnosed medical disorders such as coronary artery disease, hypothyroidism, nephrotic syndrome, liver disorders, etc
- Patients suffering from any other chronic psychiatric illness
- Pregnancy, lactation and use of oral contraceptive pills.

Methods

This study is a cross-sectional study of 100 subjects, of which 50 patients are schizophrenics and remaining 50 are age- and sex-matched controls.

During the period of study, 50 out of 62 patients of schizophrenia screened fulfilled the selection criteria. Similarly 50 out of 58 age-and sex-matched healthy volunteer controls fulfilled the selection criteria. Excel (Microsoft Office 2007) and statistical package for social sciences software packages were used for data entry and analysis and significance level of $P < 0.05$ [Figure 1].

RESULTS

Fourteen (28%) patients in schizophrenia group ($n = 50$) and six (12%) subjects in control group ($n = 50$) had MetS.

Socio-demographic profile of cases and controls

Statistically significant difference was found in domicile and education of the patient in the patient group when compared with the control group. Number of subjects

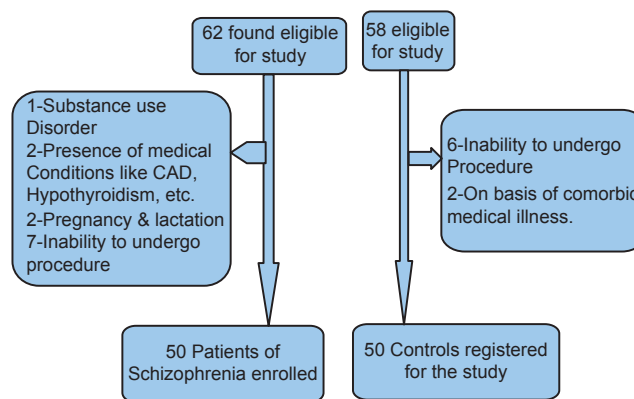


Figure 1: Profile of patients enrolled in the study to assess the relation of schizophrenia and second-generation antipsychotic

residing in urban area was more in control group and was more educated as compared to patient group. Among patient group, majority of subjects were residing in rural area and were educated upto 10th class. There was no significant difference observed in religion, marital status, and socio-economic status of patient and control groups [Table 1].

Risk factor profile of cases and controls

The mean values of serum triglyceride were higher than normal range in patient group and within normal range in control group. There was statistically significant difference in mean serum triglyceride of patient and control groups. The mean serum triglyceride of schizophrenia (153.41 ± 57.26) was significantly higher ($P < 0.05$) as compared to control group (127.94 ± 30.88) [Table 2].

Comparison of clinical variables of patients having metabolic syndrome and patients without metabolic syndrome [Table 3]

MetS was associated in patients with longer duration of illness (DOI), but this did not reach a statistically significant level.

Duration of taking antipsychotics between patients having MetS to those without MetS was statistically significant.

Statistically significant difference was found between both the patient groups who were taking first- and second-generation antipsychotics (SGAs).

No. of patients on haloperidol – 6.-No MetS.

No. of patients on trifluoperazine – 3.-No MetS.

No. of patients on clozapine – 5.-All having MetS.

No. of patients on olanzapine – 30.-9 having MetS.

No. of patients not taking any drugs – 6.-No MetS.

Comparison of body mass index in patients having metabolic syndrome and patients without metabolic syndrome

The mean body mass index (BMI) was high in patients having MetS and was in normal range in patients without MetS. Mean scores of BMI were significantly higher (i.e., more number of obese patients) in patients having MetS as compared to those without MetS [Table 4].

Comparison of metabolic syndrome parameters in patients having metabolic syndrome and patients without metabolic syndrome

The waist circumference of patients of schizophrenia

having MetS (93.60 ± 7.36) was observed to be significantly ($P < 0.0001$) higher in comparison to those without MetS (77.82 ± 9.33).

The mean fasting blood sugar of patients having MetS was observed to be significantly ($P = 0.0054$) higher in comparison to those without MetS.

The mean serum triglyceride of patients having MetS was observed to be significantly ($P < 0.0001$) higher as compared to those without MetS [Table 5].

DISCUSSION

In a case-control study of out-patients on antipsychotics versus age-and gender-matched controls, Mackin *et al.*^[6] found that the prevalence of MetS was 33.3% in schizophrenia group ($n = 90$) and 11.9% in control group. The study by Mattoo and Singh^[7] in this issue has addressed the problem of MetS in psychiatric inpatients in a hospital scenario. This research is timely considering that there is no prior published work on MetS in psychiatric inpatients in India. The findings of these studies are comparable to this study. In this study, the prevalence of MetS was 28% in schizophrenia group and 12% in control group.

Two studies from north India published during 1994 and 2000 showed a prevalence of obesity 17% (Ludhiana)^[8] and 15% (Kashmir)^[9] respectively. In another study conducted by Martin *et al.*^[10] had shown that prevalence of obesity was found significantly higher in patients with schizophrenia as compared to control. Similar findings were observed in the study conducted by De Hert *et al.*^[11] In this study, 19 (38%) patients in schizophrenia group and 18 (36%) in control group have increased waist circumference (i.e., obesity). Mean values of waist circumference in schizophrenia group ($82.24 + 11.30$) were higher as compared to control group ($81.67 + 10.56$). However, statistically significant difference was not found.

One study which was conducted in 2002^[10] has shown higher fasting blood glucose in drug-naïve patients of schizophrenia as compared to controls. The study had

Table 1: Socio-demographic profile of cases and controls

Characteristics	Cases (%)	Controls (%)	P value
Age (in years)			
20-30	20 (40)	19 (38)	0.66
31-40	15 (30)	19 (38)	
41-50	15 (30)	12 (28)	
Gender			
Male	31 (62)	32 (64)	0.83
Female	19 (38)	18 (36)	
Marital status			
Married	41 (82)	40 (80)	0.79
Unmarried	9 (18)	10 (20)	
Religion			
Hindu	48 (96)	44 (88)	0.14
Muslim	2 (4)	6 (12)	
Domicile			
Rural	24 (48)	14 (28)	0.03
Urban	26 (52)	36 (72)	
Socio-economic status			
Upper	1 (2)	3 (6)	0.49
Upper middle	9 (18)	9 (18)	
Lower middle	21 (42)	25 (50)	
Upper lower	17 (34)	10 (20)	
Lower	2 (4)	3 (6)	
Education			
Illiterate	19 (38)	8 (16)	0.04
Upto middle	5 (10)	3 (6)	
Upto senior sec	12 (24)	21 (42)	
Graduate and above	14 (28)	18 (36)	

Statistically significant difference was found in domicile and education of the patient in the patient group when compared with the control group, Number of subjects residing in urban area was more in control group and was more educated as compared to patient group, Among patient group, majority of subjects residing in rural area and were educated upto 10th class, There was no significant difference observed in religion, marital status, and socio-economic status of patient and control groups

Table 2: Risk factor profile of cases and controls

Risk factor for metabolic syndrome	Schizophrenia (n=50) mean (SD)	Control (n=50) mean (SD)	P value
Waist circumference (cm)	82.24 (11.30)	81.67 (10.56)	0.79
Fasting BGL (mg/dL)	87.47 (20.37)	84.83 (12.50)	0.43
Serum HDL (mg/dL)	40.25 (7.28)	42.74 (8.11)	0.11
Serum triglycerides (mg/dL)	153.41 (57.26)	127.94 (30.88)	0.01
Blood pressure systolic (mm of Hg)	123.84 (11.81)	120.32 (14.09)	0.18
Blood pressure diastolic (mm of Hg)	77.12 (7.68)	76.32 (9.11)	0.64
BMI (kg/m ²)	22.55 (4.19)	22.30 (3.35)	0.74

BGL: Blood glucose level, HDL: High density lipoprotein, BMI: Body mass index, SD: Standard deviation, The mean values of serum triglyceride were higher than normal range in patient group and within normal range in control group, There was statistically significant difference in mean serum triglyceride of patient and control groups, The mean serum triglyceride of schizophrenia (153.41 ± 57.26) was significantly higher ($P < 0.05$) as compared to control group (127.94 ± 30.88)

Table 3: Comparison of clinical variables of patients having metabolic syndrome and patients without metabolic syndrome

Clinical variables	Schizophrenia		Significance
	Pts with MetS (n=14) (%)	Pts without MetS (n=36) (%)	
Duration of illness			$\chi^2=1.76$
<6 months	-	4 (8)	df=2
7-12 months	1	3	P=0.416
>1 year	13 (26)	29 (59)	
Duration of taking antipsychotics			$\chi^2=6.14$
No treatment	-	6 (12)	df=2
<6 months	-	6 (12)	P=0.046
>6 months	14 (28)	4 (48)	
Antipsychotics used			$\chi^2=8.33$
1 st generation	-	9 (18)	df=2
2 nd generation	14 (28)	21 (42)	P=0.016
No treatment	-	6 (12)	

MetS was associated in patients with longer duration of illness but this did not reach a statistically significant level, Duration of taking antipsychotics b/t patients having MetS to those without MetS was statistically significant, Statistically significant difference was found b/t both the patient groups who were taking first- and second-generation antipsychotics, No. of patients on haloperidol-6.-No MetS. No. of patients on trifluoperazine-3.-No MetS. No. of patients on clozapine-5.-all having MetS. No. of patients on olanzapine-30.-9 having MetS. No. of patients not taking any drugs-6.-No MetS, MetS: Metabolic syndrome, Pts: Patients

Table 4: Comparison of body mass index in patients having metabolic syndrome and patients without metabolic syndrome

BMI	Schizophrenia		Significance
	Pts with MetS (n=14)	Pts without MetS (n=36)	
BMI			$t=3.7864$
Mean	25.74	21.31	df=48
SD	3.06	3.93	P=0.0004

The mean BMI was higher in patients having metabolic syndrome and was in normal range in patients without metabolic syndrome, Mean scores of BMI were significantly higher (i.e., more number of obese patients) in patients having metabolic syndrome as compared to those without MetS, BMI: Body mass index, MetS: Metabolic syndrome, Pts: Patients, SD: Standard deviation

reported that prevalence of diabetes was 15% higher in patient group as compared to controls. The prevalence of Fasting Blood Sugar (18% schizophrenia and 4% in controls) in patients of this study was significantly higher than the general population. Mean values of fasting blood sugar in schizophrenia group (87.47 + 20.37) were higher as compared to control group (84.83 + 12.50). Statistically significant difference was not observed between control group and schizophrenia.

Study conducted by De Hert *et al.*^[12] had shown that prevalence of hyperlipidemia was found significantly higher in patients with schizophrenia as compared to control. In this study, 20 (40%) patients in schizophrenia group and 10 (20%) subjects in control group have increased serum triglyceride.

Table 5: Comparison of metabolic syndrome parameters in patients having metabolic syndrome and patients without metabolic syndrome

Met parameters	Pts with MetS (n=14)	Pts without MetS (n=36)	Significance
Waist circumference (in cm)			$t=5.66$
Mean	93.60	77.82	df=48
SD	7.36	9.33	P=0.0001
Fasting blood sugar (in mg/dL)			$t=2.9128$
Mean	106.96	82.48	df=48
SD	46.86	12.68	P=0.0054
Serum HDL (in mg/dL)			$t=0.9404$
Mean	38.68	40.84	df=48
SD	4.86	8.01	P=0.3517
Serum triglyceride (in mg/dL)			$t=4.4884$
Mean	203.52	134.75	df=48
SD	62.39	42.42	P≤0.0001
Systolic blood pressure (in mmHg)			$t=0.4319$
Mean	125	123.38	df=48
SD	10.54	12.38	P=0.6678
Diastolic blood pressure (in mmHg)			$t=0.4319$
Mean	79.57	79.57	df=48
SD	9.77	9.77	P=0.6678

HDL: High density lipoprotein, MetS: Metabolic syndrome, Pts: Patients, SD: Standard deviation

Proportion of subjects having increased serum triglyceride was significantly higher ($P < 0.05$) in schizophrenia group as compared to control group. Thirty-six (72%) patients in schizophrenia group and 22 (44%) subjects in control group have low serum HDL. Proportion of subjects having low serum HDL was significantly higher ($P < 0.05$) in patient group as compared to control group. Also in this study, mean values of serum High Density Lipoprotein in schizophrenia group (40.25 + 7.28) were lower as compared to control group (42.74 + 8.11), but statistically significant difference was not observed. Mean values of serum triglyceride of schizophrenia group (153.41 + 57.26) were significantly higher ($P < 0.05$) as compared to control group (127.94 + 30.88).

The study by D J Raina, DS Jamwal^[13] involving 2216 individuals among rural adults of Jammu, prevalence of hypertension was 13%; females 14.71%; males 11.19% showing a strong association between gender and hypertension ($P < 0.02$). (Criteria: $\geq 140/90$ mm of Hg) among males and females, To our best efforts, we are not able to find the studies which could mention about the prevalence of hypertension in psychiatric patients in India in relation to MetS. Comparing these studies with our study showed that 11 (22%) patients in schizophrenia group and 11 (22%) subjects in control group have higher than

normal blood pressure ($\geq 130/85$ mm Hg). Low incidence of hypertension in both study and control group may be because the sample size was small and relatively younger age group was taken. Mean values of systolic blood pressure (SBP) ($123.84 + 11.81$) as well as diastolic blood pressure (DBP) ($77.12 + 7.68$) of schizophrenia group were higher as compared to control group (SBP - 120.32 ± 14.09 ; DBP - 76.32 ± 9.11). Statistically significant difference was not observed.

Study conducted by Thakore *et al.*^[10] in 2002 in which they found that patients of schizophrenia have higher BMI ($26.7 + 1.1$ kg/m²) as compared to controls ($23.5 + 0.8$ kg/m²). Study conducted by De Hert *et al.*^[2] has also shown that BMI was higher in patients having MetS and its prevalence increased with increasing DOI. This study also showed that mean values of BMI were found higher in schizophrenia group ($22.55 + 4.19$) as compared to control group ($22.30 + 3.35$). Statistically significant differences were not observed.

Geographical and ethnic variation can also account for lower rate of prevalence. Statistically significant difference was observed in domicile and education of schizophrenic group. Patients having MetS belong more in rural area than in urban area and were more educated as compared to patient group. Statistically significant differences were not observed in other socio-demographic variables such as gender, religion, and socio-economic status of both the patient groups. The possible reasons for this finding may be small sample size.

Although studies have not mentioned directly about relationship of age with MetS, but it has been postulated that prevalence of MetS varies directly with the DOI,^[14] therefore, the prevalence of MetS was found in higher age group. In one study, the prevalence of MetS was found 37% in long-term schizophrenics, with a mean age of 45 years.^[15] Also in this study, the mean age of patients having MetS was higher (36.92 years) as compared to the patients without MetS (34.75 years). The lower prevalence (28%) of MetS found in this study may partly due to younger age group.

In one study,^[2] mean values of SBP, DBP, waist circumference, S. HDL, S. TG, and BMI were found significantly higher in patients having MetS as compared to patients without MetS. Our study also shows similar results. Waist circumference, fasting blood sugar, triglycerides, and BMI were found significantly higher in patients having MetS as compared to patients without MetS. Both SBP and DBP were found higher and HDL was lower in patients with MetS as compared to patients

without MetS. However, the differences were not statistically significant.

Although the mean DOI was longer in patients with MetS as compared to the patients without MetS, the difference did not reach to the statistically significant level. The above-mentioned finding is similar to the conclusions of the study conducted by Ford *et al.*,^[2] where the prevalence of MetS was higher in patients with longer DOI.

Thirty-eight patients (76%) were taking antipsychotics for more than 6 months of duration, in which 14 patients (28%) were found to have MetS. No patient has MetS who had taken antipsychotics for <6 months of duration. These findings are more or less similar to one group of investigators who found that people with schizophrenia (both those with first episodes and those chronically exposed to conventional medications) have more than three times as much intra-abdominal fat as controls matched for age, gender, and lifestyle and that 6 months of treatment with either olanzapine or risperidone, although increasing BMI does not significantly increase visceral fat stores.^[10,16]

Recent studies suggest that the syndrome is increased in people with schizophrenia and in particular in those taking the SGA drugs such as olanzapine and clozapine.^[17,18]

Our study also shows similar results. All the patients having MetS were taking SGAs (clozapine and olanzapine). This was statistically significant ($P < 0.05$). Statistically significant differences were not observed among the majority of socio-demographic parameters between patient and control group. Maximum numbers of subjects were in the age group of 21-30 years in all the groups and males were more than females in schizophrenia group. Statistically significant difference ($P < 0.05$) was found in domicile and education of the patient group. Control group was more significantly ($P < 0.05$) belongs to urban area when compared with the patient group. Subjects in control group were more educated as compared with patient group. The possible reason for this difference may be because of illness, the subjects of patient group were not able to study or have stopped their studies. There was no significant difference observed in religion, marital status, and socio-economic status of patient group and control group. The reason behind this may be because all the subjects of patient as well as control group belong to the same geographical area.

These patients have further increased the risk of MetS due to unhealthy lifestyle issues, e.g., poor diet, lack of exercise, and cigarette smoking, which are known to have higher prevalence in these patients than in the general population.

Findings of this study could not be corroborated because the studies on this category of patients are deficient in India.

CONCLUSIONS

The awareness of metabolic complications in schizophrenia should encourage clinicians and psychiatrists to screen first episode of psychosis for the predisposing factors of MetS. Once they have been prescribed medication, patients should be monitored on a regular basis. The blood tests and oral glucose tolerance, practical anthropometric measures of intra-abdominal fat such as waist circumference and waist-to-hip ratio should be taken. Psychiatrists should screen for such metabolic disturbances if patients have no access to primary care. Finally, simple lifestyle advice on the virtues of a balanced diet and regular exercise should be routinely given to all patients, as these are still the most effective ways of preventing diabetes and its related complications.

These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic complications for which these patients are at increased risk.

LIMITATIONS

Due to the constraints of a time bound study and because of the stringent selection criteria, the sample size was small and hence the results are subjected to type II error and they cannot be generalized. The study is a cross-sectional study and to further assess the effect of psychotropic medication on MetS, longitudinal studies are needed.

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