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Low incidence of metabolic syndrome in patients taking atypical antipsychotic in Eastern India

Abstract

Background: Atypical antipsychotics, widely used in many psychiatric diseases, are known to cause metabolic syndrome (MetS). But, there is sparse of prospective study to see the effect of atypical antipsychotics causing MetS in drug naïve or drug free patients among the Indian population. This study aimed to determine the incidence of MetS and change in individual risk factor for MetS in schizophrenia and mood disorder patients after three months of receiving atypical antipsychotics. **Method:** Sixty patients of schizophrenia (n=40) and mood disorders (n=20) were screened at the baseline and all of them were prospectively followed up for the occurrence of MetS after three months. **Results:** By applying the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) modified criteria for Asian, the incidence of MetS was found to be 11.66%. When analysing the individual risk factor for MetS, the mean value from baseline to follow-up was weight (in kg) 58.55±10.03 to 59.80±10.24 (p<0.001), waist circumference (cm) 80.52±6.33 to 81.43±6.42 (p<0.001), systolic blood pressure (mm/Hg) 113.93±8.28 to 117.53±10.89 (p<0.001), diastolic blood pressure (mm/Hg) 74.80±7.31 to 78.32±6.79 (p<0.001), fasting blood glucose (mg/dl) 86.23±12.02 to 91.35±13.04 (p<0.001), triglyceride (mg/dl) 97.32±31.41 to 101.25±34.38 (p<0.001), high-density lipoproteins (HDL) (mg/dl) 48.07±4.98 to 48.05±4.57 (p=0.951). **Conclusion:** Our study suggests that incidence of MetS in Indian population was 11.66% after three months of using atypical antipsychotic drugs in patients with schizophrenia or mood disorder. The change in mean value in the individual risk factor for MetS was statistically significant. Long-term follow-up studies are required to identify the real burden of MetS after using atypical antipsychotic drugs.

Keywords: Prospective Studies. Schizophrenia. Mood Disorders.

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INTRODUCTION

The co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease like abdominal obesity, hyperglycaemia, hyperlipidaemia, and hypertension suggest the existence of metabolic syndrome (MetS).[1,2] Other names applied to this constellation of findings have included syndrome X, the insulin resistance syndrome, the deadly quartet, or the obesity dyslipidaemia syndrome.[3] The definition of MetS, given by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) and also, the International Diabetic Federation (IDF) is well-documented.[4]

The prevalence of MetS, as defined by ATP III, was evaluated on 8814 adults in the United States, participating in the Third National Health and Nutrition Examination Survey (NHANES III 1988-1994).[5] The overall prevalence was 22% with an age dependent increase (6.7, 43.5, and 42.0% for the ages 20-29, 60-69, and more than 70 years respectively).

It was also found that in moderately obese people (body mass index [BMI] 30-35), insulin sensitivity varied and those with greatest level of insulin resistance had the highest blood pressure (BP), triglyceride (TG), and plasma glucose level and lowest high-density lipoprotein (HDL) concentration despite of the equal level of obesity.[6]

Many psychotropic drugs like antidepressant, mood stabilizer, and antipsychotic have weight gain as potential side effect which may ultimately lead to hypertension, diabetes, and lipid abnormalities. Measurement of waist circumference (WC) may be used as a risk indicator. Additionally, patients with schizophrenia are at increased risk of cardiovascular disease.[7] The prevalence of insulin resistance in patients with schizophrenia has been estimated to be 1.5 to two times that in the general population. This may lead to type 2 diabetes mellitus and these would increase the risk of mortality and morbidity.[8] Approximately 50% of women and 66% of men with bipolar disorder are overweight and one of the factors for this is using drugs which can cause weight gain. It appears that gaining weight can increase risk of relapse into new episode.[9] Use of atypical antipsychotics has been cited as one of the reasons for increased prevalence of MetS in schizophrenia. Lifetime prevalence of MetS is in the range of three to 26% in drug naïve patients while the same reaches up to 69% in medicated patients with schizophrenia.[10-12] The prevalence of MetS in bipolar disorder in the world population ranges from six to 70.3% depending upon variables, such as diagnostic criteria, co-morbidities, ethnic group, and sex.[13] In bipolar patients, MetS co-morbidity is associated with a more complex disease, a less favourable response to treatment, and adverse conveys and outcome, such as increased risk for depressive symptoms and episode, and risk of suicide.[14,15]

In India, there is sparse of scientific data on incidence of MetS in patients on atypical antipsychotics till 2007-2008.[16] Although cross-sectional studies have evaluated the prevalence of MetS in patients with psychotic illness, data from longitudinal studies are limited.[17] Mackin *et al.*[18] opined that prospective studies are needed to explore the precise relationship between antipsychotic drugs, glucose homeostasis, obesity, and MetS. Gautam and Meena[19] opined that no studies had been performed so far to find out the attribution of atypical antipsychotic in the causation of MetS in drug naïve patients suffering from schizophrenia who were physically fit and metabolically normal. Grover *et al.*[20] found that in bipolar affective disorder (BPAD), longitudinal studies were lacking.

Fewer prospective studies are reported from India which dealt with the finding of incidence of MetS in drug naïve schizophrenia and mood disorder patients after taking atypical antipsychotics. Therefore, the current study aimed to study the incidence of MetS in schizophrenia and mood disorder patients after three months of receiving atypical antipsychotics (monotherapy) and also, any changes in individual risk factors for MetS after receiving atypical antipsychotics.

MATERIAL AND METHODS

Study design and recruitment

This is a comparative, non-blinded, single centred, prospective and parallel groups, experimental study. It was conducted in outpatient department (OPD) clinic and indoor of psychiatry department of Kalinga Institute of Medical Sciences, Bhubaneswar, India over a period of 20 months (from December 2014 to July 2016). The study was approved by the Institutional Ethics Committee. Written informed consent of all patients participating in the study was obtained. Inclusion criteria included those who aged 18 years and above but, not more than 45 years, who have been diagnosed with schizophrenia or mood disorder with psychotic symptoms (diagnosed by a consultant according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] diagnostic criteria),[21] both inpatients and outpatients, and who had not taken any oral antipsychotics or depot preparation for last three months. Exclusion criteria included patients with baseline evidence of any component of MetS, with other co-morbid psychiatric or organic mental conditiona, pregnant woman or history of pregnancy in last six months, patients with alcohol dependence and substance misuse disorder other than tobacco, any other chronic illness (rheumatoid arthritis [RA], pulmonary tuberculosis [TB], protein energy malnutrition [PEM]), and who are unable to provide consent.

The method of sampling was purposive one. Total 97 patients were considered and screened; out of them, 24 could not be included in the study for not giving consent (two), low HDL (eight), high triglyceride (three), high blood pressure (BP) (four), high fasting blood glucose (FBG) (four), and increased waist circumference (three). Out of 73 patients, 13 patients did not follow-up to three months and ultimately 60 patients were taken for the final study.

Data collection

Important demographic (age, sex), anthropometric (weight, height, BMI, and WC), clinical (systolic and diastolic BP [SBP and DBP]) and biochemical parameter (serum TG, HDL, and FBG) were collected at baseline and monitored after three months.

Criteria for MetS

According to ATP III Asian guidelines, a person is sufferer with MetS if he or she fulfils at least three out of five criteria, namely higher WC for male >90 cm and for female >80 cm; HDL for male <40 mg/dl and for female <50 mg/dl; TG >150 mg/dl; FBG ≥110mg/dl; BP ≥130/85 (SBP/DBP) mm of hg. According to IDF guidelines, the cut-off values for some of the these parameters are changed and defined as WC for male ≥94 cm and for female 80 cm; HDL for male <40 mg/dl and for female <50 mg/dl; TG ≥150mg/dl; FBG ≥100mg/dl; BP ≥130/85 (SBP/DBP) mm of Hg.[22]

Statistical analysis

The collected data of the above-mentioned parameters was compiled and entered in Microsoft Excel 2007. Prevalence of MetS along with individual as well as multiple risk factors was reported. Descriptive statistics for continuous parameter was reported through mean±standard deviation (SD) and reported as frequency (%) for categorical parameters. Association of any two categorical variables was assessed either through chi-square test or Fisher's exact test. As all the continuous parameters followed normal distribution, these parameters were compared for any changes from baseline to follow-up through paired t-test. All the statistical analysis was done by using standard statistical software Stata version 13.1. A p-value of <0.05 was considered statistically significant. The clinical relevance of the results in the light of statistical analysis was discussed.

RESULTS

Seventy five patients were taken into the study of which two patients did not give consent. Out of remaining 73 patients, 13 patients did not follow-up for three months (drop-out patients). Accordingly, a total of 60 patients were taken into consideration for the final study.

Out of 60 patients, 24 patients (40%) were female and 36 (60%) were male. Out of these 60 patients, 20 patients were diagnosed as having mood disorder (33.3%) and 40 were diagnosed as schizophrenia (66.6%).

Also, while using antipsychotic drugs among these 60 patients, 26 patients (43.33%) received olanzapine with mean dose of 10±2.5 mg/day and 34 patients received risperidone (56.66%) with mean dose of 4±0.2 mg/day.

When we looked into the socioeconomic background among 60 patients, 19 patients came from middle and upper middle socioeconomic class. Rest 41 patients came from lower middle and lower economic class. Based on place of residence of the patients, it was observed that 28 patients came from urban background whereas 32 patients came from rural background.

Emergence of MetS

According to NCEP ATP III modified criteria for Asian, it was observed that seven patients (11.66%) had developed MetS (Table 1). Within these seven patients, three patients (8.33%) were male and four (16.67%) patients were female. Also, following this criteria, we observed five patients (25%) had developed MetS from mood disorders category while two patients (five per cent) had developed MetS from schizophrenia category. When we classify the incidence of MetS in antipsychotic groups, we observed two patients from olanzapine group (out of 26 patients who received olanzapine, i.e. 7.7%) had MetS, while five patients from risperidone group (out of 34 patients who received risperidone, i.e. 14.7%) had developed MetS (Table 1).

Based on IDF criteria, it was observed that six patients had MetS (ten per cent). Out of these six patients, five were female and one patient was male which account for 20.83% and 2.77% among the total female and male subjects respectively. From the mood disorder group, it was seen that four out of 20 patients (20%) had developed MetS and in schizophrenia group, two out of 40 persons (five per cent) had developed MetS. Also, while using olanzapine on the 26 patients, we found one patient had developed MetS (3.85%) and using risperidone on 34 patients, five patients had developed MetS (i.e. 14.70%).

Table 2 shows the prevalence of individual risk factor based on two different Asian and IDF criteria. According to Asian criteria, the most prevalent risk factor is WC (23.3%) and based on IDF criteria, the most prevalent risk factor is FBG (26.7%) followed by SBP (21.7%), DBP (20%), and HDL (20%).

As shown in Table 3, change in mean weight (mean difference of 1.25 kg) was found to be statistically significant. Similarly, mean difference in waist circumference from baseline was significantly increased (mean difference of 0.91 cm) after three months. SBP and DBP both increased significantly ($p<0.001$). The change in the mean FBG was increased from 86.23 mg/dl to 91.35 mg/dl ($p<0.001$). Also, mean serum TG level was significantly ($p<0.001$) increased during follow-up assessment (from 97.32 mg/dl to 101.25 mg/dl). In case of serum HDL level, the change from baseline (48.07 mg/dl) to (48.05 mg/dl) was not statistically significant ($p=0.951$).

DISCUSSION

Severe mental illness (SMI) are associated with a significant excess of physical co-morbidity and as such represents a major public health concern.[23-25] While atypical antipsychotics (risperidone and olanzapine) were the main drugs for schizophrenia patients, sometimes we had to use trihexyphenidyl (for extrapyramidal symptoms), benzodiazepines (to sedate the patients or if there is complaint of insomnia) to make the patients stable. But, in case of mood disorder patients, where most of the patients were diagnosed as BPAD (85%), we had to use mood stabilizer medicines like divalproex sodium and lithium, benzodiazepines, or sometimes, trihexyphenidyl.

Rest of the mood disorder patients were diagnosed as severe depressive episode with psychotic symptoms. The few unipolar depressed patients who were included in our study were having psychotic symptoms. So, all these patients

Table 1: Association of different characteristics with and without MetS based on NCEP ATP III modified Asian criteria

Parameter	Total	With MetS n (%)	Without MetS n (%)	p-value
Sex				0.422
Male	36	3 (8.3)	33 (91.7)	
Female	24	4 (16.7)	20 (83.3)	
Type of drug				0.688
Olanzapine	26	2 (7.7)	24 (92.3)	
Risperidone	34	5 (14.7)	29 (85.3)	
Type of problem				0.036
Mood disorder	20	5 (25.0)	15 (75.0)	
Schizophrenia	40	2 (5.0)	38 (95.0)	

MetS=Metabolic syndrome, NCEP ATP III=Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

Table 2: Risk factor profile based on Asian and IDF criteria

Parameter	Asian criteria n (%)	IDF criteria n (%)
WC	14 (23.3)	7 (11.7)
HDL	12 (20.0)	12 (20.0)
TG	7 (11.7)	7 (11.7)
FBG	9 (15.0)	16 (26.7)
SBP	13 (21.7)	13 (21.7)
DBP	12 (20.0)	12 (20.0)

IDF=International Diabetic Federation, WC=waist circumference, HDL=high-density lipoprotein, TG=triglyceride, FBG=fasting blood glucose, SBP=systolic blood pressure, DBP=diastolic blood pressure

Table 3: Changes among the risk factor of MetS

Parameter	Baseline assessment Mean±SD	Follow-up assessment Mean±SD	p-value
Weight (in kg)	58.55±10.03	59.80±10.24	<0.001
WC (in cm)	80.52±6.33	81.43±6.42	<0.001
HDL (mg/dl)	48.07±4.98	48.05±4.57	0.951
TG (mg/dl)	97.32±31.41	101.25±34.38	<0.001
FBG (mg/dl)	86.23±12.02	91.35±13.04	<0.001
SBP (mm of Hg)	113.93±8.28	117.53±10.89	<0.001
DBP (mm of Hg)	74.80±7.31	78.32±6.79	<0.001

MetS=Metabolic syndrome, SD=standard deviation, WC=waist circumference, HDL=high-density lipoprotein, TG=triglyceride, FBG=fasting blood glucose, SBP=systolic blood pressure, DBP=diastolic blood pressure

were given atypical antipsychotic along with antidepressant (selective serotonin reuptake inhibitor [SSRI] or serotonin and norepinephrine reuptake inhibitor [SNRI]), and benzodiazepine. No depressive patients without psychotic symptoms were there in our study.

The current study used NCEP ATP III modified criteria for Asian to evaluate the number of patients having MetS. Gautam and Meena[19] observed in their study that 11.66% patients developed MetS after using atypical antipsychotics (olanzapine, risperidone, and clozapine) after four months of treatment using ATP III diagnostic guidelines. The results are almost similar to our observations but, there are two differences. In ATP III criteria, WC would be more than 102 cm in case of male and 88 cm in case of female. But, in modified ATP III criteria for Asian, the limits of WC are more than 90 cm in male and 80 cm in female.

Another important difference between these two prospective studies was that the current study involved both schizophrenia and mood disorders whereas Gautam and Meena[19] had studied only schizophrenia patients. In our study, after three months, two patients with schizophrenia developed (among 40 schizophrenia patients) MetS which was five per cent.

Though this is well-proven fact that a patient is sufferer with MetS when three out of five risk factors are positive (either NCEP ATP III, modified ATP III, adopted ATP III, or IDF criteria), current study also demonstrated that when a person fulfils two out of five criteria then may be identified as "at risk of MetS" or "some MetS" as described by Chandel *et al.*[26] These persons are more prone for developing MetS in near future. For this reason, six more patients who are "at risk for MetS" were identified. Accordingly, apart from the patients with MetS among schizophrenia group (five per cent), additional patients "at risk for MetS" were observed as 7.89% (i.e. 12.89%). These data are in accordance with the incidence data of Gautam and Meena[19] (11.66% incidence of MetS).

Applying ATP III modified criteria for Asian, a total of five out of 20 mood disorder patients (25%) were diagnosed as MetS which is comparatively high than the incidence among schizophrenia group. The probable cause being high genetic predisposition to hypertension, type 2 diabetes mellitus or impaired glucose tolerance or hyperlipidaemia. Theses information could not be obtained from the patients or their family members (informants) during initial screening due to their lack of knowledge and information about these diseases in their family tree. Rural background, low socioeconomic status, low level of education could be other factors for not getting proper information. Other than these causes under mood disorders and major depressive disorders, either mood stabilizers (like lithium or valproate) or antidepressants were also added. Most of these drugs may contribute to weight gain which can increase WC or even other metabolic parameters. Mirtazapine increasing TG level is a well-documented fact.

Unfortunately, randomised controlled trial of antipsychotics drugs among mood disorder patients is not reported. Accordingly, finding from the current study are not being compared.

Barnwal and Oza[16] had shown in their prospective study on different psychiatric patients (mood disorders being the commonest diagnosis; others were schizophrenia, brief psychotic disorders, etc.), a considerable change in weight (increased), FBG (increased), and significant rise in serum TG. But, the investigators did not estimate the incidence of MetS.

Another prospective longitudinal study of MetS in patients with bipolar disorders and schizophrenia was done by Malhotra and Kulhara.[17] They had opined that 40% patients with BPAD and 32% with schizophrenia have MetS at baseline and after six months of follow-up, the prevalence becomes 48% and 41.4% for BPAD and schizophrenia respectively. Chandel *et al.*[26] conducted a prevalence study in drug naïve BPAD (cross-sectional study). They found 14% prevalence of MetS (point prevalence) and "some MetS" (two risk factors positive out of five) were found in 29% patients. They concluded that high prevalence of MetS was only 14% but the individual metabolic abnormalities were even higher in bipolar individuals even before the time of initiating pharmacological treatment. There may be some inherent risk factors for MetS in BPAD patients and the effect of medication may further compound that risk.

van Winkel *et al.*[27] studied 60 bipolar patients and found prevalence of MetS of 16.07%. Though there are differences in the percentage of occurrence of prevalence (old and new cases) with that of incidence (new cases) but, still sometimes prevalence indicates the trend of incidence. Majority of the studies (though in abroad) had shown high prevalence rate of MetS in BPAD patients. This indirectly

shows that incidence rate of MetS in BPAD patients might be higher which is similar to our findings.

To evaluate the changes in individual continuous parameters (followed normal distribution), paired t-test is applied. The mean weight from baseline to follow-up is found to be significantly increased but practically not meaningful. Gautam and Meena[19] had shown in their study that mean change in weight in risperidone and olanzapine group (n=60) together was from (kg) 58 to 60.38. So, increase in weight in both the groups combined was 2.38 kg in four months. Finding from the current study is comparable to this referred study.

The land mark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)'s first phase study showed that the weight gain potential in olanzapine is approximately two pounds.[28] So, in three months, it would be around six pounds which is nearly three kg. Bustillo *et al*.,[29] in a four-month study, found that the mean weight gain in patients receiving olanzapine was 3.5 kg. The small difference found in the result between the two studies may be due to the fact that the current study dealt with subjects receiving both olanzapine and risperidone, and the duration of follow-up in the current study was also three month relatively smaller.

The change in WC from baseline to follow-up was increased by 0.91 cm ($p<0.001$) in our subject group. Gautam and Meena[19] had shown in their study that mean value of WC (in cm) in baseline (for olanzapine and risperidone group together) changed from 77.85 to 79.86 after four months of follow-up. The difference is higher and may be because of relatively longer follow-up. Meyer *et al*.[30] commented from their prospective data from phase 1 of CATIE Schizophrenia Trial that the mean increase in WC after three months in olanzapine group was 0.7 inch (1.77 cm) and that of risperidone group was 0.4 inch (1.01 cm). These reports are also very close to our findings.

The change in mean SBP and DBP from baseline to follow-up were increased by 3.60 mm/Hg and 3.52 mm/Hg respectively ($p<0.001$). Both the change in SBP and DBP do not show much clinical relevance. Gautam and Meena[19] had found that mean difference in SBP was 5.05 mm Hg and no change in mean difference in DBP after four months of follow-up. The current study has similar observation.

Similar change of 5.12 mg/dl is observed statistically significant in FBG. The increase in mean difference physiologically is not very meaningful until it crosses the diabetes range (i.e. 126 mg/dl). Gautam and Meena[19] found that after four months, the mean change in FBG was 17.04 mg/dl. This data seems to be clinically relevant. The difference in observation may be due to the change of ethnicity, food habit, dose of antipsychotics, and duration of antipsychotics (one month more than our study period). In another open level prospective study by Neredumilli and Rao[31] (in olanzapine group), mean difference changes of FBG (mg/dl) after three months was 5.3 mg/dl.

The mean difference of 3.93 mg/dl in serum TG does not have much clinical relevance. Gautam and Meena[19] had opined that after four months the mean difference in TG (in olanzapine and risperidone group) was 20.75 mg/dl. This value is clearly more clinically significant than our value. Neredumilli and Rao[31] had observed in their prospective study of 12 weeks that the mean change in TG value was 24.6 mg/dl in olanzapine group and 11.58 mg/dl in risperidone group.

The change in HDL level from baseline to follow-up was not statistically significant. Naredumilli and Rao[31] had shown that the mean difference of HDL level after three months was 0.85 mg/dl ($p=0.33$), which was similar to our study. Meyer *et al*.,[30] from a prospective data from phase 1 in CATIE Schizophrenia Trial had observed that the decrease in mean HDL level after three months in olanzapine and risperidone group was 2.3 and 0.7 (mg/dl) respectively. This finding was not much different from the current study observation. Whereas Gautam and Meena[19] had shown 8.52 mg/dl decrease in mean HDL level after four months of follow-up. This finding has its own clinical relevance.

Summary and conclusion

Current study suggests that incidence of MetS in Indian population in those who are sufferer with schizophrenia or mood disorders is about 11.66% after three months of using atypical antipsychotic drug. However, the mean change in the individual risk factor for MetS was not clinically significant after three months. Studies with long-term follow-up are required to identify the real model for risk factor of MetS after using atypical antipsychotic drugs.

Limitation of the study

The data on life style, such as diet habit and its pattern, physical activity, smoking and alcohol could not be obtained. The detailed information on patients' socioeconomic and demographic characteristics, family structure and history could not be considered properly which may have meaningful association with MetS. There is a need for prolonged follow-up at six months, 12 months, and even more. Study with more subjects will be powerful and may give additional meaningful association.

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