International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Metabolic Syndrome and Psychosis: Role of Atypical Antipsychotics

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Abstract: ***Introduction: The present study was conducted with the objective of assessing the incidence of metabolic syndrome in patients of psychosis (schizophrenia, schizoaffective, delusional disorders and other psychotic disorders) treated with atypical antipsychotics. We also aimed to study the various metabolic syndrome parameters in these patients i.e. dyslipidemia, hyperglycemia, weight-changes and hypertension. Materials & Methods: A hospital based prospective observational study was conducted in patients receiving atypical antipsychotics at Department of Psychiatry of a tertiary care centre. A total of 30 consecutive patients diagnosed with schizophrenia, schizoaffective, delusional disorders and other psychotic disorders were taken in the study after obtaining informed consent. Blood pressure, waist circumference, fasting blood sugar levels, fasting triglyceride levels and fasting high density lipoprotein-cholesterol level (HDL-cholesterol) were investigated and recorded on a pre-designed proforma at baseline and at 6 and 12 weeks follow up. Results: Out of the 30 cases, 16 were of schizophrenia, 8 were of acute of transient psychotic disorder, 4 have schizoaffective disorder and 2 had delusional disorder. 16. Mean triglyceride levels, waist circumference and fasting blood sugar were significantly increased during each follow up in the course of treatment at 6 weeks and 12 weeks($p<0.05$) while no significant changes were seen in SBP and DBP at 12 weeks follow up ($p>0.05$). HDL levels were significantly reduced at 12 weeks follow up ($p<0.05$). Overall prevalence of metabolic syndrome in patients on Atypical Antipsychotics was 23.3%. Conclusion: Second-generation antipsychotics cause significant changes in the metabolic parameters, increasing the chances of developing metabolic syndrome and associated disorders like diabetes mellitus type-II and cerebrovascular accidents. In high risk patients, careful selection of second generation antipsychotic is important. Regular screening may help to timely identify the early metabolic changes and avoid further complications.***

Keywords: Atypical Antipsychotics, Metabolic Syndrome, Psychosis, Schizophrenia

1. Introduction

Metabolic syndrome (MetS) represents a cluster of physiological and anthropometric abnormalities characterized by abnormally elevated glucose level, obesity, hypertension, elevated triglycerides and low high-density lipoprotein-cholesterol (HDL-c).[1]

Individuals with metabolic syndrome have a 3 fold increased risk for the development of cerebrovascular stroke and coronary artery diseases, 6 fold increased risk for cardiovascular mortality and a 5 fold higher risk of diabetes.[2,3] Prevalence of metabolic syndrome as defined by NCEP ATP III and other criteria ranges from about 11% to 41% in different regions of India.[4-7]

Metabolic syndrome and its components, including obesity, glucose intolerance, dyslipidemia, and hypertension, are highly prevalent among patients with severe mental illnesses[8-10] and have been associated with increased risk of cardiovascular disease.[11]Patients of schizophrenia have been reported to have 2 – 4 times higher prevalence of metabolic syndrome[12,13]whereas patients of bipolar disorders have 30% higher prevalence compared to the general population[14].

Atypical or second-generation antipsychotics (SGAs) have been an important addition to the armamentarium of pharmacologic treatments for schizophrenia and other psychiatric disorders. However, they are among the factors implicated in the development of metabolic syndrome in this susceptible population. Highest risk of metabolic syndrome has been reported with clozapine and olanzapine, intermediate risk with iloperidone, quetiapine, risperidone, paliperidone, sertindole & zotepine and the least risk has been reported with amisulpride, aripiprazole, asenapine, lurasidone and ziprasidone.[15] However, no antipsychotic drug is believed to be free of metabolic side effects; even those usually without such effects may cause them in specific situations.

The information available in the existing literature is limited regarding prevalence of metabolic syndrome in Indian population and it may also be different from their counterparts in other regions of the world. Hence, the present study was carried out at a tertiary care centre to assess the burden of metabolic syndrome in patients on atypical antipsychotics.

2. Materials and Methods

Study Design: Prospective Observational study conducted in patients receiving atypical antipsychotics.

Study Duration: 1st October 2014 to 31st September 2016

Study Area: The study was conducted at a tertiary hospital with a fully-fledged Department of Psychiatry of a tertiary care Institute**.**

Sampling Technique & Sample Size: Consecutive type of non-probability sampling was used for selection of study subjects. A total of 30 consecutive patients diagnosed with schizophrenia, schizoaffective, delusional disorders and other psychotic disorders according to International classification of Disease (ICD-10): Diagnostic criteria for Research,[16] and started on atypical anti-psychotics after

fulfilling of inclusion and exclusion criteria were taken in the study after obtaining informed consent.

Inclusion Criteria

1) All patients of psychosis diagnosed by ICD-10 criteria.
2) Patient age group between 18 years and 60 years.
3) Both male and female patients.
4) Both IPD and OPD patients.
5) All patients consenting to study.
6) Patient should be either treatment naïve or have stopped all treatment for period of at least 6 months.

Exclusion Criteria

1) Patient with any pre-existing medical Co-morbidity under treatment including DM, HTN, IHD etc.
2) Known case of metabolic syndrome.
3) Patients on mood stabilizers or on any atypical antipsychotic.
4) Known case of hypothyroidism.
5) Female Patients who are pregnant.
6) Patients with history of substance abuse.

3. Methodology

Patient attending our outpatient department as well as admitted in the indoor ward were assessed for any of the psychotic disorders i.e. schizophrenia, schizoaffective, delusional disorders and other psychosis by ICD-10.[16] The diagnosis of all the patients were confirmed by consultant psychiatrist at Psychiatric Department of our Institute. Patients who were started on atypical antipsychotics like Olanzapine, Risperidone, etc. were enrolled for the study. Relevant Baseline investigations were recorded for all patients. On follow up at 6 weeks and 12 weeks, abdominal girth (measured midway between the lowest rib and the iliac crest with the subjects standing using a tape with a spring loaded mechanism to standardize tape tension during measurement), blood pressure, fasting blood sugar levels, fasting triglyceride levels and fasting high density lipoprotein- cholesterol level (HDL-cholesterol) were investigated and recorded on a pre-designed proforma. Pharmacy and medical records were reviewed to obtain demographic, clinical and drug treatment data.

Tools Description

1) Socio demographic sheet: All the socio demographic and clinical variables were recorded on a pre-designed proforma.
2) Measuring tape for abdominal girth.
3) Sphygmomanometer for Blood pressure.
4) Automated Ex-350 for fasting blood sugar levels.
5) Automated Adott for Triglycerides level
6) Automated Adott for HDL cholesterol level.

Statistical Analysis: All the collected data was entered in Microsoft Excel Sheet 2007.The data was then transferred and analyzed using SPSS ver. 21. Qualitative data was represented in the form of frequency and percentage while quantitative data was represented using Mean +/- S.D. Appropriate statistical tests were applied based on the type and distribution of data. A p-value of < 0.05 was taken as level of significance.

4. Results

Most of the subjects were between 31-50 years of age (66.67%) with mean age of 36.6 years. Male pre-dominance was observed in study group with 60% males to 40% females. Out of the 30 cases, 16 were of schizophrenia, 8 were of acute of transient psychotic disorder, 4 have schizoaffective disorder and 2 had delusional disorder. Olanzapine was given in 36.7% cases, clozapine was given in 23.3% cases and 40% cases were on Risperidone. Mean triglyceride levels, waist circumference and fasting blood sugar were significantly increased during each follow up in the course of treatment at 6 weeks and 12 weeks($p<0.05$) while no significant changes were seen in SBP and DBP at 12 weeks follow up ($p>0.05$) (Table 1). HDL levels were significantly reduced at 12 weeks follow up ($p<0.05$). All patients had normal triglyceride levels at baseline while 3 and 6 ($p<0.05$) patients had high TGs at 6 weeks and 12 weeks post treatment. Patient with low HDL levels increased to7 ($p<0.05$) and to 12 ($p<0.01$) at 6 weeks and 12 weeks follow up.Subjects with increased waist circumference (> 102 cm for males &> 88 cm for females) did not increased significantly (p-0.77, p-0.31).Patient with high fasting sugar levels increased to 4 and to 6 ($p<0.05$) at 6 weeks and 12 weeks follow up.A total of 5 patients had high blood pressure at the time of start of treatment and at 6 week follow up there was 1 new patient having high blood pressure which increased to 3 at 12 weeks(p-0.53) follow up (i.e. total 3 patients increased from baseline).

(Table 2). Overall the prevalence of metabolic syndrome in patients on Atypical Antipsychotics was 23.3% (Table 3).

5. Discussion

Antipsychotic medicines are routinely used in the treatment of psychosis. Atypical or second generation antipsychotics can cause metabolic disturbances. The frequency of these adverse events vary between different atypical antipsychotics. In present study, prevalence of metabolic syndrome in patients on Atypical Antipsychotics was observed as 23.3%. A prospective interventional study by Gautam S et al. from Jaipur, India has shown high prevalence of metabolic syndrome in patients treated with second generation antipsychotics. Out of 120 patients studied, 11.66% developed metabolic syndrome after 4 months of treatment.[17]Another recently published study in 100 subjects (50 patients of schizophrenia and 50 controls) from India has also shown higher prevalence of metabolic syndrome in patients suffering from schizophrenia (28%) compared to general population (12%).[18]In another similar study by Chuki et al., overall the prevalence of metabolic syndrome was 22.1%.[19] Various other studies reported the prevalence of metabolic syndrome as 11.7 - 48.1% in patients on antipsychotic therapy.[20-23]

Reduced methylenetetrahydrofolate reductase (MTHFR) activity, resulting in altered metabolism of folate and hyperhomocysteinemia, may be the cause for cardiovascular disease in patients receiving atypical antipsychotics. The results from a small study have suggested the MTHFR 677C/T variant may predispose patients to atypical antipsychotic associated metabolic derangements.[24]

Hyperglycemia

In present study, mean blood sugar levels were significantly increased during each follow up in the course of treatment at 6 weeks and 12 weeks ($p<0.05$). Patient with high fasting sugar levels increased to 4 and to 6 ($p<0.05$) at 6 weeks and 12 weeks follow up.

Dwyer DS et al. have shown that certain antipsychotic agents, including clozapine, olanzapine and chlorpromazine can inhibit glucose uptake via interactions with glucose transporter proteins in in-vitro studies whereas other agents such as haloperidol, had a marginal effect on glucose transport.[25] Risperidone can also interact with these intracellular proteins, but the limited lipophillic nature of this agent results in reduced tissue to plasma concentration ratio, suggesting that intracellular protein interactions as well as intracellular drug concentrations may be critical to the prediction of drug effects in this area. Differing effects on glucose transport can be hypothesized to underlie the clinical observation of different adiposity-independent antipsychotic drug effects on insulin sensitivity.[17]In a study by Chuki et al. the elevated fasting blood glucose was observed in 80.7% of patients.[19] In a study by Gautham et al., olanzapine (10mg/day) treated group showed mean increase of 8.8 mg/dl in FBS after 6 months of treatment which was statistically significant ($p<0.05$).[17]Our observations were also similar to those of Lindenmayer JPet al.,[26] who also compared the change in blood glucose and lipid profile after giving atypical antipsychotics to his patients for 14 weeks. Perez Iglasias[27]found a similar pattern of increase in the fasting glucose level after a 12-week study with treatment naïve patients. Newcomer[28]found that patients treated with olanzapine and clozapine had the highest propensity to develop glucose intolerance. A recent systematic review and metaanalysis concluded that all atypical antipsychotic drugs (excluding aripiprazole, ziprasidone and amisulpride for which there was insufficient data to be included in the analysis) were associated with a 30% increased risk of diabetes as compared to typical antipsychotic drugs in people with schizophrenia.[29] Various other studies reported the prevalence of hyperglycemia as 24.6 – 41.6% in patients on antipsychotic therapy.[21-23]

Dyslipidemia

In present study, mean triglyceride levels significantly increased during each follow up in the course of treatment at 6 weeks and 12 weeks ($p<0.05$). HDL levels were significantly reduced at 12 weeks follow up ($p<0.05$). All patients had normal triglyceride levels at baseline while 3 and 6 ($p<0.05$) patients had high TGs at 6 weeks and 12 weeks post treatment. Patient with low HDL levels increased to 7 ($p<0.05$) and to 12 ($p<0.01$) at 6 weeks and 12 weeks follow up.

The mechanisms underlying the changes in lipid parameters associated with antipsychotic therapy have been little studied although a number of possible mechanisms have been suggested. Epidemiological studies in the general population provide a variety of data showing that weight-gain and obesity increase the risk of dyslipidemia. Obesity and weight gain are associated with increased triglyceride and LDL-cholesterol levels and reduced HDL-cholesterol. Antipsychotic agents differ markedly in their weight gain potential, suggesting that the effects on lipid levels seen with antipsychotic agents may primarily be related to their effect on bodyweight and adiposity.[30] Other factors may also play a role in the development of treatment associated dyslipidemia. The development of glucose intolerance would be expected to affect lipid levels, as insulin resistance is a key factor in the pathophysiology of dyslipidemia. A few reports of substantial elevations in triglyceride levels with only modest weight gain raise the possibility of a direct antipsychotic effect on lipid levels by some as yet unknown mechanism.[13,31]

Newcomer et al.[28] also showed significant ($p<0.05$) increase serum cholesterol (21.1 mg/dl), serum LDL (20.5 mg/dl) and serum triglyceride (30 mg/dl) after 24 weeks treatment of olanzapine (5 mg/day). Gautam S et al.,[17] also reported significant ($p<0.05$) changes in lipid profile at end of 3 months. Chuki et al. reported the prevalence of hypertriglyceridemia as 48.4% in their study.[19] Various other studies reported the prevalence of hypertriglyceridemia as 39.3 – 67.7% and prevalence of low HDL cholesterol as 23.6 - 72.6% in patients on antipsychotic therapy.[20-23] Though changes in metabolic parameters are different in different studies, may be due to cultural and ethnic study showed variation, difference in the follow up periods and sample size. Comparative analysis of all groups in the present that there was statistically significant changes in serum triglyceride and serum HDL at the end of 3 months treatment.

Waist Circumference

In present study, mean waist circumference significantly increased during each follow up in the course of treatment at 6 weeks and 12 weeks. While Subjects with increased waist circumference (> 102 cm for males &> 88 cm for females) did not increased significantly (p-0.77, p-0.31).

Almost all the antipsychotics are associated with weight gain, while olanzapine and clozapine have been identified as the drugs causing maximum weight gain. The mechanisms by which antipsychotic medications produce weight gain may include stimulating appetite, reducing physical activity and directly impairing metabolic regulation. The pathophysiology of weight gain is mediated through monoaminergic, cholinergic and histaminergic neurotransmission. Differential affinities for the serotonin 5-$HT_{2C}$and H_1 receptors may explain the greater weight gain seen with clozapine and olanzapine.[17]Previous studies have suggested that second-generation antipsychotics vary in their propensity to induce weight gain; clozapine and olanzapine produce the most weight gain, quetiapine and risperidone produce intermediate weight gain while aripipirazole and ziprasidone has the least propensity to do so.[32] Similar results were achieved by studies conducted by Perez Iglesias[27] and Saddichhaet al.[33]Similar changes in waist circumference was seen in studies by Gautam et al.[17]and Chuki et al.[19]Chuki et al. observed the prevalence of elevated waist circumference in 41.9% patients after second-generation antipsychotic therapy.[19]Various other studies reported the prevalence of elevated waist circumference as 61.6% - 98.4% in patients on antipsychotic therapy.[20-23]

Blood Pressure

In present study, no significant increase was seen in mean SBP and DBP at 12 weeks follow up. A total of 5 patients had high blood pressure at the time of start of treatment which increased to 8 at 12 week follow up ($p>0.05$).

Atypical antipsychotics have been shown to be associated with weight gain, dyslipidemia, and type 2 diabetes.[19-23]These adverse effects act synergistically in patients with schizophrenia, who have an elevated cardiovascular risk. Studies suggest that people with schizophrenia are two to three times more likely to die from cardiovascular disease than members of the general population.[34] Patients with schizophrenia are predisposed to obesity, type 2 diabetes, abnormal variations in cardiac rate, and sudden death, independent of medication use.[35-37]In a study by Henderson et al.,[38] there was a significant increase in systolic blood pressure ($p <0.01$) and diastolic blood pressure ($p <0.01$). Chuki et al., observed the prevalence of hypertension in their study as 48.4% compared.[19]Various other studies reported the prevalence of elevated waist circumference as 40 - 61.1% in patients on antipsychotic therapy.[20-23]

6. Conclusion

Second-generation antipsychotics cause significant changes in the metabolic parameters, increasing the chances of developing metabolic syndrome and associated disorders like diabetes mellitus type-II and cerebrovascular accidents. In high risk patients, careful selection of second generation antipsychotic is important. Regular screening may help to timely identify the early metabolic changes and avoid further complications. Collaboration between psychiatrist and endocrinologist/diabetologist is recommended for avoiding these complications and in turn improving the outcome of schizophrenia management.

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Tables

Table 1: Distribution of patients according to mean change in metabolic syndrome parameters

Laboratory Findings		Mean	SD	p-value*
Triglycerides	Baseline	97.47	23.94	<0.05
	6 weeks	106.47	29.04	
	12 weeks	114.70	27.86	**<0.05**
HDL	**Baseline**	46.87	5.53	**<0.05**
	6 weeks	42.93	6.23	
	12 weeks	40.53	5.68	**<0.05**
Waist Circumference	**Baseline**	86.70	8.08	**<0.05**
	6 weeks	89.60	8.65	
	12 weeks	91.47	8.59	**<0.05**
FBS	**Baseline**	87.50	12.29	**<0.05**
	6 weeks	95.23	13.77	
	12 weeks	104.12	12.77	**<0.05**
SBP	**Baseline**	112.32	13.11	**0.19**
	6 weeks	115.32	15.45	
	12 weeks	121.10	17.87	**0.06**
DBP	**Baseline**	77.32	9.76	**0.21**
	6 weeks	80.01	8.90	
	12 weeks	82.21	9.78	**0.07**

*1st and 2nd p-values are for baseline vs 1st f/u and baseline vs 2nd f/u comparisons

Table 2: Distribution of patients as per derangement in metabolic syndrome parameters at each follow up

Derangement in MS parameters after treatment (n-30)		N	%	p-value*
Triglycerides (>150)	6 weeks	3	10.0%	0.23
	12 weeks	6	20.0%	<0.05
HDL (<50: F; <40:M)	6 weeks	7	23.3%	<0.05
	12 weeks	12	40.0%	<0.01
Waist Circumference (>102:M; > 88:F)	6 weeks	2	6.7%	0.77
	12 weeks	4	13.3%	0.31
FBS (>110)	6 weeks	4	13.3%	0.19
	12 weeks	6	20.0%	<0.05
BP (>130/85)	6 weeks	1	3.3%	1.00
	12 weeks	3	10.0%	0.53

*p-values are for baseline vs 1st f/u and baseline vs 2nd f/u comparisons

Table 3: Prevalence of Metabolic syndrome

Metabolic Syndrome (12 week follow up)	N	%
Yes	7	23.3%
No	23	76.7%
Total	30	100.0%