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METABOLIC EFFECTS OF ANTIPSYCHOTIC TREATMENT IN SCHIZOPHRENIA

Psychiatry

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ABSTRACT

BACKGROUND: It is well established that morbidity and mortality of Schizophrenia is significantly increased due to the metabolic derangements caused by anti-psychotic medications which in turn are potent cardiovascular risk factors. Despite this widespread knowledge of metabolic risks of antipsychotic treatment, the metabolic parameters of the patients are rarely taken into consideration while prescribing antipsychotic medications in India.

AIM: To determine the effects of antipsychotic treatment on the metabolic parameters in drug naïve patients of schizophrenia.

METHOD: Eighty consecutive drug naive schizophrenia patients were assessed for 05 metabolic parameters which form the criteria of metabolic syndrome (NCEP- ATPIII). These parameters were again assessed after 06 months of treatment in the same set of patients. The data was then analyzed for changes in metabolic parameters in context of treatment with first and second generation antipsychotics.

RESULT: Our study found that there were significant changes in the metabolic parameters after 06 months of treatment with anti-psychotic medications.

CONCLUSION: Antipsychotic medications, both first and second generation, cause significant derangements in the metabolic parameters. Thus, metabolic parameters should always be taken into consideration before starting of antipsychotic treatment as well as during follow up.

KEYWORDS

Metabolic derangements, drug naive schizophrenia.

INTRODUCTION

Morbidity due to schizophrenia has reduced steadily since the advent of newer antipsychotics, but mortality of these patients has increased over time and one of the main contributing factors is association of schizophrenia with physical illnesses like metabolic syndrome and coronary artery disease (1). The frequency of metabolic syndrome has been found to be 2–4 times higher in a group of people with schizophrenia, and treated with both atypical and typical neuroleptics, than in an appropriate reference population (2). With the advent of antipsychotic drugs, the relationship between schizophrenia and metabolic abnormalities became further confounded as some of the newer anti-psychotics, can promote weight gain and insulin resistance (3). But, despite this widespread knowledge of metabolic risks of antipsychotic treatment, the metabolic parameters of the patients are rarely taken into consideration while prescribing antipsychotic medications.

As per the third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (4), the metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM) are-

1. Waist Circumference > 102 cm in men and 88 cm in women,
2. Serum triglyceride level ≥ 150 mg/dL,
3. High density lipoprotein (HDL) < 40 mg/dL in men and < 50 mg/dL in women,
4. Blood pressure ≥ 130/85 mm Hg, or
5. Fasting serum Glucose level ≥ 110 mg/dL.

The metabolic syndrome (syndrome X, insulin resistance syndrome) is said to occur if 03 or more of the above criteria are fulfilled. The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by an incompletely understood defect in insulin action. (5) (6). Development of insulin resistance and impaired glucose metabolism is usually a gradual process, beginning with excess weight gain and obesity. The mechanisms that link obesity with insulin resistance, however, are still uncertain.

In this study we assess the 05 metabolic parameters which form the criteria of metabolic syndrome (NCEP- ATPIII) in drug naïve patients of schizophrenia and follow them up for fist 06 months of their treatment to determine the changes in these parameters due to the effects of the antipsychotic treatment.

AIM

To determine the effects of antipsychotic treatment on the metabolic parameters in drug naïve patients of schizophrenia.

MATERIALS AND METHOD

This study which was carried out in department of the psychiatry in a tertiary care hospital in Eastern India over a period of 01 year after due approval by institutional ethics committee. Eighty consecutive adult patients, who were diagnosed as having Schizophrenia as per ICD-10 criteria and who themselves/whose relatives provided written informed consent, were included in the study. Patients having past/family history of diabetes or cardiovascular disease, history of chronic medical illnesses, taking medications known to affect body glucose or lipids, pregnancy, or history of concurrent substance use were excluded from the study.

Initially, Socio-demographic data of the selected patients such as age, gender, lifestyle, occupation, duration of illness were noted and entered on excel sheet. These patients were then assessed for waist circumference, serum triglyceride level, serum high density lipoprotein, systolic and diastolic blood pressure and fasting serum glucose level which form the criteria for metabolic syndrome as per the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (2). Each case was assessed for these metabolic parameters again after 06 months of antipsychotic treatment. These findings were carefully recorded and the data collected were analyzed using appropriate statistical analysis method.

RESULTS

The age of the study population ranged from 16yrs to 68 yrs with mean age being 36yrs. Total number of female patients 41 (51.2%) and that of male patients was 39 (48.8%). Among these, 76.9% were females, only 23.1% were males. There were 38 (47.5%) housewives, 30 (37.5%) serving soldiers, 7 (8.8%) retired persons, and 5 (6.2%) students among the study population. 35 (43.8%) of the patients entering the study had an active life style while 45 (56.2%) of them led more of a sedentary lifestyle. Regarding the duration of illness prior to start of treatment, 43 (53.8%) of the patients had symptoms since 03

months, 28 (35.0%) of them had symptoms since 04 to 06 months, 8 (10.0%) of them had symptoms since 07 to 09 months, and only 1 (1.2%) had duration of illness of 10 to 12 months prior to start of treatment.

Among the 92 drug naïve schizophrenia patients recruited in this study, 05 were lost to follow up, while, 07 had to be prescribed more than one antipsychotic or other psychotropic drugs too. Thus 12 such patients were dropped from the study. At entry, among the 80 patients who were included in the study, the mean waist circumference was 92 cm, the mean fasting blood sugar level was 94 mg/dl, the mean fasting serum triglyceride level was 140 mg/dl, the mean fasting serum high density lipoprotein level was 42 mg/dl, the mean systolic BP was 127.85 mm Hg and the mean diastolic BP was 83.60 mm Hg. 26 (32.5%) participants were found to fulfill the NCEP ATP-III criteria for metabolic syndrome. There was significant increase in mean waist circumference (2.85cm), mean fasting blood sugar (9.83mg/dl), and mean fasting serum triglycerides (16.450mg/dl), after 06 months' treatment and now almost 46 (57.5%) of the patients fulfilled the criteria of metabolic syndrome. The metabolic parameters which found deranged at the entry were found to worsen even more with antipsychotic treatment, those parameters which were normal at the start also worsened.

Metabolic parameters for all cases at baseline as per ATP-III Criteria (table-3)

metabolic parameters	Mean	Std dev
WC	92	± 9.9
FBS	94	± 13
FTGS	140	± 52.4
FHDL	42	± 8.1
SBP	127.85	±15.676
DBP	83.60	±9.474

Metabolic parameters for all cases after 06 months of anti psychotic treatment

metabolic parameters	Mean	Std dev
WC	95	± 10
FBS	104	± 16
FTGS	157	± 35.6
FHDL	41	± 7
SBP	130.02	±10.304
DBP	85.58	± 6.346

Changes in metabolic parameters for all cases after 06 months of antipsychotic treatment

Metabolic parameters	Change from baseline	P value	Significance
WC	2.85	<0.001	Significant
FBS	9.83	<0.001	Significant
FTGS	16.45	0.001	Significant
FHDL	-0.86	0.145	Not Significant
SBP	2.18	0.338	Not Significant
DBP	1.98	0.144	Not Significant

Effect of Aripiprazole on metabolic components

For the 16 patients treated with Aripiprazole, the changes in mean waist circumference, mean fasting serum triglyceride level, mean fasting serum HDL level, mean systolic BP and the mean diastolic BP before and after treatment were not statistically significant. However, the increase in mean fasting blood sugar level before and after treatment was statistically significant.

	Aripiprazole (n=16)			
	After treatment with Aripiprazole	Before treatment		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
SBP	127 ± 7.8	132.25 ± 13.22	0.227	Not Significant
DBP	83.63 ± 5.76	87.13 ± 6.45	0.120	Not Significant
WC	97.5 ± 10.13	95.81 ± 11.16	0.071	Not Significant
FBS	102.5 ± 14.67	94.81 ± 15.92	0.024	Significant
FTGS	154.38 ± 30.54	151.81 ± 75.49	0.844	Not Significant
FHDL	42.75 ± 7.78	43.12 ± 8.03	0.756	Not Significant

Effect of Haloperidol on metabolic components

For the 18 patients treated with Haloperidol, the changes in mean waist circumference and mean fasting blood sugar level before and after treatment were found to be statistically significant. However, the increase in mean fasting serum HDL level, mean fasting serum fasting TGS level, mean systolic BP, and the mean diastolic BP before and after treatment were found to be not statistically significant.

	Haloperidol (n=18)			
	After treatment with haloperidol	Before treatment with haloperidol		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
SBP	129.89 ± 12.9	132.22 ± 16.22	0.606	Not Significant
DBP	85.78 ± 6.36	85.11 ± 9.85	0.804	Not Significant
WC	98.56 ± 8.87	96.06 ± 7.92	0.015	Significant
FBS	110.83 ± 26.45	97.17 ± 12.48	0.029	Significant
FTGS	162.56 ± 27.61	150.33 ± 40.68	0.109	Not Significant
FHDL	40.94 ± 4.56	40.94 ± 4.82	1.000	Not Significant

Effect of Olanzapine on metabolic components

For the 30 patients treated with Olanzapine, the increase in mean waist circumference, mean fasting blood sugar level, mean systolic BP and mean diastolic BP before and after treatment were found to be statistically significant. However, the increase in mean fasting serum HDL level and mean fasting serum fasting TGS level before and after treatment were found to be not statistically significant.

	Olanzapine (n=30)			
	After treatment with olanzapine	Before treatment with olanzapine		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
SBP	132.93 ± 10.34	123.07 ± 11.71	0.003	Significant
DBP	86.47 ± 7.31	80.93 ± 7.25	0.006	Significant
WC	90.6 ± 9.12	87.6 ± 9.18	0.000	Significant
FBS	103.63 ± 9.17	94.4 ± 12.57	0.000	Significant
FTGS	154.17 ± 42.56	140.53 ± 52.45	0.061	Not Significant
FHDL	40.93 ± 6.6	42.3 ± 8.61	0.189	Not Significant

Effect of Risperidone on metabolic components

For the 16 patients treated with Risperidone, the increase in mean waist circumference, mean fasting blood sugar level and mean fasting serum fasting TGS level before and after treatment were found to be statistically significant. However, the increase in mean fasting serum HDL level, mean systolic BP and mean diastolic BP before and after treatment were found to be not statistically significant.

	Risperidone (n=16)			
	After treatment with risperidone	Before treatment with risperidone		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
SBP	127.75 ± 8.42	127.5 ± 21.61	0.971	Not Significant
DBP	85.63 ± 4.91	83.38 ± 13.75	0.596	Not Significant
WC	94.31 ± 8.59	90.19 ± 8.76	0.011	Significant
FBS	98.31 ± 9.18	89.56 ± 9.6	0.009	Significant
FTGS	157.69 ± 36.4	117.31 ± 27.16	0.000	Significant
FHDL	40.62 ± 9.37	42 ± 10.62	0.451	Not Significant

DISCUSSION

Even studies in the pre-neuroleptic era clearly suggested that schizophrenia might be a risk factor for the development of diabetes (7). Various mental disorders, e.g. depression, bipolar affective disorder and schizophrenia have been reported to be associated with increased risk of diabetes (8), (9). Studies have showed an increased liability for people with schizophrenia to develop metabolic abnormalities even in the absence of antipsychotic medication, and have reported increased visceral adiposity, elevated glycaemia and higher cortisol levels in first-episode patients before treatment (10), (11), (12). The causes of these metabolic derangements are likely to reflect a mix of genetic and environmental factors and the interactions between these. Unaffected first-degree relatives of people with schizophrenia have high rates of type 2 diabetes mellitus (19-30%), pointing to a genetic association between these two disorders (13). Many studies have reported this increased risk for diabetes in first-degree relatives of patients with schizophrenia (10), (14), (15). Another possibility to consider is that people with schizophrenia on

average have a lifestyle which increases their risk for the development of Metabolic Syndrome: sedentary lifestyle, lack of regular physical activity, poor food intake, substance use and high rates of smoking (10), (15). Part of these lifestyle factors are influenced by aspects of the illness such as negative symptoms and vulnerability to stress.

The frequency of metabolic syndrome has been found to be 2–4 times higher in a group of people with schizophrenia, and treated with both atypical and typical neuroleptics, than in an appropriate reference population, in a cohort study of 269 patients, aged 20-69 years, with schizophrenia living in Northern Sweden (2). Comparison of mean weight changes and relative percentages of patients experiencing specific levels of weight increase from controlled, randomized clinical trials indicates that weight gain liability varies significantly across the different second generation antipsychotic agents (16) (17). Clozapine and olanzapine treatment are associated with the greatest risk of clinically significant weight gain, with other agents producing relatively lower levels of risk. Risperidone, Quetiapine, amisulpride and zotepine generally show low to moderate levels of mean weight gain and a modest risk of clinically significant increases in weight. Ziprasidone and Aripiprazole treatment are generally associated with minimal mean weight gain and the lowest risk of more significant increases (16) (17). Published studies including uncontrolled observations, large retrospective database analyses and controlled experimental studies, including randomized clinical trials, indicate that the different second-generation antipsychotics are associated with differing effects on glucose and lipid metabolism. In general, the rank order of risk observed for the second-generation antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of insulin resistance, dyslipidemia and hyperglycemia (17)

Thus as far as effects of anti-psychotic agents as metabolic risk factor are concerned, our findings generally mirror findings of similar as well as large scale studies done all over the world (18). In our study, if we consider metabolic syndrome as per NCEP ATP-III criteria, almost half of the patients, who did not fulfill the criteria of metabolic syndrome at the entry and treated with either olanzapine or risperidone, developed it after 06 months of treatment. Similarly, almost one fourth of the patients, who did not have metabolic syndrome at the entry point and treated with haloperidol, developed it after 06 months of treatment with this first generation anti psychotic agent. But none of the patients, who did not have metabolic syndrome at the entry point and treated with Aripiprazole, developed it after 06 months of treatment. Instead, one patient who did have metabolic syndrome at entry to the study, and treated with Aripiprazole, did not fulfill the criteria for the same after 06 months of treatment. Thus the effect of olanzapine, risperidone and haloperidol in promoting and Aripiprazole in somewhat resisting the development of metabolic syndrome was found to be quite evident and statistically significant in our study. We also found that the antipsychotic agents in general, cause a statistically significant increase in waist circumference, fasting blood sugar and fasting serum triglyceride level. They also cause a decrease in fasting serum high density lipoprotein level and an increase in systolic and diastolic BP, but these changes were not found to be statistically significant. As metabolic syndrome alone predicts about 25% of all new onset cardiovascular disease, and the presence of metabolic syndrome is also highly predictive of new-onset diabetes (19). Our finding may thus explain at least part of the excess mortality of schizophrenic patients due to cardiovascular disease.

A systematic review and meta-analysis comparing diabetes risk for different antipsychotics in people with schizophrenia by M. Smith et al (2008) found that there is tentative evidence that the second-generation antipsychotics are associated with a small increased risk for diabetes compared with first generation antipsychotics in people with schizophrenia (20). Our study also found similar results as evidenced by the fact that second generation antipsychotic like olanzapine and risperidone were associated with much more metabolic derangements (emergence of metabolic syndrome in about 50% of the drug naïve patients with schizophrenia who did not have metabolic syndrome at entry into the study) compared to those treated with first generation antipsychotic, haloperidol (emergence of metabolic syndrome in about 25% of the drug naïve patients with schizophrenia who did not have metabolic syndrome at entry into the study). Thus we can say that neither first generation antipsychotics nor second generation antipsychotics are free from metabolic side effects and differ only slightly in their liability to produce metabolic syndrome.

Lesson Learnt-

Assessment of metabolic parameters of each schizophrenia patient should be done before commencement of antipsychotic treatment and their treatment should be tailored by considering the propensity to produce metabolic derangements of the drug being prescribed for treatment of such patients. Such assessment may lead to better treatment outcomes by decreasing the morbidity and mortality due to physical illnesses among these patients.

CONCLUSION-

Antipsychotic medications, both first and second generation, cause significant derangements in the metabolic parameters in schizophrenia patients. Thus, the metabolic parameters of each patient should be assessed before commencement of antipsychotic treatment and matched against the propensity to produce metabolic derangements of the drug being considered for treatment in each such patient.

Declaration of Conflicting Interests-

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