International Journal of Research in Medical Sciences
Kumar H et al. Int J Res Med Sci. 2014 May;2(2):569-574
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: 10.5455/2320-6012.ijrms20140538

Research Article

Metabolic syndrome in schizophrenia: how much is attributable to drug treatment?

Harish Kumar[1]*, Rajiv Gupta[2], Sonal Dogra[3], Rajneesh Kumar Joshi[4]

[1]Department of Psychiatry, MAMC, Agroha, Hisar, Haryana, India
[2]Department of Psychiatry, Pt BDS PGIMS, Rohtak, Haryana, India
[3]Medical Officer, Haryana Civil Medical Services, Rohtak, Haryana, India
[4]Medical Officer, National AIDS Research Institute, Pune, Maharashtra, India

Received: 6 February 2014
Accepted: 1 March 2014

***Correspondence:**
Dr. Harish Kumar,
E-mail: hari_vashisth@yahoo.co.in

ABSTRACT

Background: This study was planned to investigate new onset metabolic syndrome (MS) and its various components associated with two widely used second generation antipsychotics i.e. olanzapine and quetiapine in the management of schizophrenia using International Diabetic Federation (IDF) criteria.
Methods: A total of 60 drug naïve patients with ICD-10 diagnosis of first episode schizophrenia, divided in two groups of 30 patients each, were randomly allocated to receive two different treatments i.e. olanzapine and quetiapine. Metabolic parameters were measured at day 0, then at 6 and 12 weeks. For categorical variables, 'Chi-square test' was used for comparison between the two groups. For continuous variables student's t-test was used.
Results: At 6 weeks none of the patient, treated with olanzapine, developed Metabolic Syndrome (MS), but among quetiapine group 3.33% (1 out of 30) developed MS. At the end of 12 weeks, 20% patients (i.e. 6 out of 30) had MS in olanzapine treatment group and 10% (3 out of 30) in quetiapine treatment group.
Conclusion: Both olanzapine and quetiapine were found to cause comparable metabolic derangement and metabolic syndrome.

Keywords: Schizophrenia, First episode, Drug naïve, Olanzapine, Quetiapine

INTRODUCTION

In the last two decades, the use of second generation antipsychotics has superseded first generation antipsychotics mainly because of their lower propensity to cause the troublesome extra-pyramidal side effects and claims of efficacy in treatment of negative and cognitive symptoms. But in last few years, various metabolic complications in the form of weight gain, glucose intolerance leading to diabetes mellitus and lipid disturbances in the form of hypertriglyceridemia and low protective HDL cholesterol surfaced the clinical scenario in psychiatric practice. The increased health damages with clustering of these metabolic parameters led to the gradual concept of syndrome X, Insulin resistance syndrome and finally metabolic syndrome. Studies in different parts of world established the high prevalence of metabolic syndrome in patients of schizophrenia which was further increased by antipsychotics (second generation). Schizophrenia and other psychotic disorders decrease life expectancy by 20% with the standardized mortality rate being twice as compared to general population and cardiovascular illnesses remain the most important overall cause accounting for over 60% of the total deaths in schizophrenia.[1]

The terms "metabolic syndrome," "insulin resistance syndrome" and "syndrome X" have been used specifically to define a constellation of abnormalities that are associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease (e.g., heart disease and stroke). The prevalence of metabolic syndrome is high in first episode psychosis and increases with duration of illness.[2] Kato et al. (2004) found metabolic syndrome to be more prevalent in Hispanics compared to non-Hispanic patients of schizophrenia, showing influence of race in metabolic syndrome.[3]

Zhang et al. (2004) studied drug naive Chinese in-patients with diagnosis of schizophrenia before and following 10 weeks of antipsychotic treatment. The patient group showed significant increase in abdominal subcutaneous fat and intra-abdominal fat following antipsychotic treatment.[4] DeHert et al. (2007) assessed the prevalence of metabolic syndrome in 155 patients of first episode schizophrenia in Belgium. After treatment with second generation antipsychotics for a period of three months the occurrence of metabolic syndrome was as follow: amisulpride-6.3%; aripiprazole-0%; clozapine-45%; olanzapine-24.4%; quetiapine-19.1%; risperidone-10.8%.[5] Perez-Iglesias et al. (2007) conducted a randomized, prospective clinical trial to evaluate metabolic changes in drug-naïve patients of first-episode psychosis. Patients were assigned to haloperidol, olanzapine or risperidone treatment during 12 weeks. At the endpoint significant weight gain was observed with the three antipsychotics with mean weight gain: haloperidol=3.8 kg, olanzapine=7.5 kg and risperidone=5.6 kg. Metabolic parameters showed a worsening lipid profile with the 3 treatments.[6]

DeHert et al. (2008) compared the prevalence of metabolic syndrome in patients of first episode schizophrenia after treatment with first and second generation antipsychotics for a period of three years. There was no difference in the prevalence of metabolic syndrome between two groups at baseline. The rates of metabolic syndrome increased over time in both groups, but patients started on second generation antipsychotics had three times higher incidence rate of metabolic syndrome.[7]

Metabolic syndrome in first episode schizophrenia has also been assessed in India. Saddichha et al. (2007) conducted a double-blind, prospective study in drug naïve female patients of first episode schizophrenia. The incidence of metabolic syndrome at baseline was 3.33% which increased significantly to 31.81% at endpoint i.e. 6 weeks.[8]

Saddichha et al. (2008) found prevalence of metabolic syndrome in schizophrenia in India to be between 10-18% which was at least five times higher as compared to the matched healthy control group. Those on olanzapine had maximum prevalence of metabolic syndrome (20-25%) followed by risperidone (9-24%) and haloperidol (0-3 %).[9]

How much of these side effects are attributed by use of antipsychotics and how much are inborn to the disorder, still remains a question. There are differences in the metabolism across culture and Asian Indians compared to Caucasians have higher body fat, higher waist to hip ratio, and high intra-abdominal and subcutaneous fat. In contrast, the body mass-index, waist and hip circumference and muscle mass are lesser in Asians as compared to Caucasians. Keeping in view the marked differences in body metabolism, ethnicity, socio-cultural status, food habits and life style between our population and Caucasians, it is expected that pattern of change of metabolic parameters would be different in our population and it would be unfair to extrapolate Western data to our population. Considering the paucity of Indian studies on the relationship of metabolic syndrome with antipsychotic medications in schizophrenia, this study to examine Indian perspective of metabolic syndrome in schizophrenia and its relationship with antipsychotic medication was planned.

METHODS

Present study was conducted in the department of psychiatry, Pt B. D. Sharma PGIMS, Rohtak. A total of 60 drug naïve patients with ICD-10 diagnosis of first episode schizophrenia were randomly divided in two groups of 30 patients each to receive two different treatments i.e. olanzapine or quetiapine. Written informed consent was obtained from the patients or their guardians, emphasizing that they could withdraw from the study whenever they wished to do so, and that withdrawal from studies in no way will affect the treatment, ensuring confidentiality of the information. Consecutives patients with ICD-10 diagnosis of first episode schizophrenia were screened according to the following inclusion and exclusion criteria:

Inclusion criteria

1) Current diagnosis of schizophrenia according to ICD-10.
2) Adult patients of either sex in age group of 16-40 years.
3) A written informed consent from patient or legal representative.

Exclusion criteria

1) Patient suffering from substance induced psychotic disorder, psychotic disorder due to general medical condition, or mental retardation.
2) Patients with contraindication to antipsychotic medications e.g. hypersensitivity reaction.
3) Patients already on psychotropic medication.
4) Patients with history of hypertension, diabetes mellitus or obesity or meeting any of the component

of metabolic syndrome (IDF Criteria, ethnic-specific) at the time of first examination.
5) Family history of hypertension or diabetes mellitus.
6) Pregnant or lactating females.

The socio-demographic profile and relevant clinical details of the selected patients were recorded on the semi-structured proforma prepared for the study. The patients were followed up for a period of 6 and 12 weeks. At baseline, patients received a full clinical examination. During the clinical examination blood pressure and anthropometric measurements were obtained by use of standard protocols and techniques.[10] Three blood pressure measurements at 5 minute intervals were obtained with the participant in the seated position and mean of these measurements was recorded. Waist circumference was measured at the level of umbilicus at minimal respiration. The metabolic screening was carried out which included fasting blood sugar and lipid profile. All these assessments were done in a single session. The same protocol was repeated at 6 weeks and 12 weeks. The study patients were recruited till complete assessment of 60 patients (30 patients each in group A and group B).

International Diabetic Federation (2005) definition for metabolic syndrome (for South Asians including Indians) criteria was used to define the metabolic syndrome.[11]

The criteria include:

1. Waist circumference >90cm (men)
   80cm (women) - obligatory criterion

Plus any two of the following:

2. Triglycerides >150mg/dl
3. HDL-C <40mg/dl (men)
   <50mg/dl (women)
4. Blood pressure >130/85mm Hg
5. Fasting plasma glucose >100mg/dl

Data analysis

The data collected during the study were entered in the Microsoft excel format and was analyzed using SPSS.10 version Microsoft software. For categorical variables, 'Chi-square test' was used for comparison between the two groups. For continuous variables student's t-test was used. The P values were two tailed and probability level for significant difference was set at P <0.05.

RESULTS

No statistical difference was found between the two treatment groups as far as mean age, sex distribution, marital status and mean duration of untreated illness was concerned.

Table 1: Comparison of physical and metabolic parameters at baseline i.e. 0 week.

Baseline characteristics	Treatment group-olanzapine Mean ± SD	Treatment group-quetiapine Mean ± SD	Comparison		
			t	df	P
Weight (kg)	48.63 ± 10.36	50.43 ± 9.22	0.711	58	0.480*
WC (cm)	71.46 ± 6.07	72.98 ± 5.25	1.035	58	0.305*
FBS (mg%)	73.80 ± 11.30	77.90 ± 9.60	1.514	58	0.135*
TGL (mg%)	103.80 ± 27.72	100.17 ± 19.04	0.592	58	0.556*
HDL (mg%)	48.50 ± 5.34	49.67 ± 5.41	0.841	58	0.404*
SBP (mmHg)	113.33 ± 8.79	115.33 ± 6.44	1.005	58	0.319*
DBP (mmHg)	74.53 ± 5.11	75.47 ± 5.77	0.662	58	0.510*

*Not Significant

No statistically significant difference was found when baseline mean values of corresponding characteristics were compared between two groups, using unpaired t-test (Table 1).

New onset MS

At 6 weeks none of the patient, treated with olanzapine, developed MS, but among quetiapine group 3.33% (1 out of 30) developed MS (Table 2a).

At the end of 12 weeks, 20% patients (i.e. 6 out of 30) had MS in olanzapine treatment group and 10% (3 out of 30) in quetiapine treatment group (Table 2b).

Table 2a: New onset MS at 6 weeks.

MS	Treatment group olanzapine (n=30)	Treatment group Quetiapine (n=30)
Yes	0 (0%)	1 (3.33%)
No	30 (100%)	29 (96.67%)

Table 2b: New onset MS at 12 weeks.

MS	Treatment group olanzapine (n=30)	Treatment group Quetiapine (n=30)
Yes	6 (20%)	3 (10%)
No	24 (80%)	27 (90%)

Occurrence of various components of MS among treatment groups at 6 weeks and 12 weeks

At 6 weeks none of the subject met Waist Circumference criteria in olanzapine treatment group, while only one male (3.33%) in quetiapine group. Maximum number of subjects met criteria for HDL i.e. 9 (30%) in olanzapine group while 11 (36.67%) in quetiapine group. 3 patients (10%) were found to meet criteria for glucose, 1 (3.33%) for TGL and none for BP in olanzapine group, on the other hand in quetiapine: glucose criteria met in 2 (6.67%), TGL in 3 (10%) and BP in 2 (6.67%) (Table 3a).

Table 3a: Components of MS at 6 weeks.

	Treatment group - olanzapine (n=30)	Treatment group- quetiapine (n=30)
BP (>130/85)	0	2 (6.67%)
HDL		
(M <40 mg/dl)	4 (13.33%)	3 (10%)
(F <50 mg/dl)	5 (16.67%)	8 (26.67%)
Total	9 (30%)	11 (36.67%)
TGL (>150 mg/dl)	1 (3.33%)	3 (10%)
FBS (>100 mg/dl)	3 (10%)	2 (6.67%)
WC		
M >90cm	0	1 (3.33%)
F >80cm	0	0

Table 3b: Components of MS at 12 weeks.

	Treatment group - olanzapine (n=30)	Treatment group- quetiapine (n=30)
BP (>130/85)	2 (6.67%)	1 (3.33%)
HDL		
(M <40 mg/dl)	10 (33.33)	7 (23.33%)
(F <50 mg/dl)	10 (33.33%)	10 (33.33%)
Total	20 (66.67%)	17 (56.67%)
TGL (>150 mg/dl)	12 (40.00%)	9 (30%)
FBS (>100 mg/dl)	5 (16.67%)	3 (10%)
WC		
M >90cm	3 (10%)	2 (6.67%)
F >80cm	3 (10%)	1 (3.33%)
Total	6 (20%)	3 (10%)

At 12 weeks maximum subjects were found to meet criteria for HDL i.e. 20 (66.67%) in olanzapine and 17 (56.67%) in quetiapine group. 12 patients (40%) met criteria for TGL, 6 (20%) for WC, 5 (16.67%) for FBS and only 2 (6.67%) for BP in olanzapine group. In quetiapine group 9 patients (30%) met criteria for TGL, 3 (10%) each for FBS and WC, and 1 (3.33%) for BP (Table 3b).

DISCUSSION

This was a prospective study and one of the few studies using such a design. Consecutive cases were taken and it was ensured that the patients were drug naïve i.e. they had not taken any psychotropic medication before. Patients who met even a single criterion of MS as defined by IDF (2005) at baseline were excluded. Only patients in the age group of 16-40 were included in the study so that confounding effect of high age could be mitigated as the prevalence of metabolic syndrome increases rapidly after age 40 and reaches over 40% at age >60 years.[12]

Patients who had presence of overt organic brain disorder, known pregnancy/lactation or known contraindications for antipsychotic medications were excluded from the study. Patients with family history of hypertension, obesity or diabetes mellitus were excluded to prevent confounding due to familial predisposition for these abnormalities.

Patients with concurrent use of any substance or other medications, which could possibly alter the metabolic homeostasis, were excluded thus neutralizing the maximum possible confounders.

Most of the studies available, addressing the metabolic side effects of various antipsychotics, are cross-sectional or even retrospective reviews. The present study, on the other hand, was extended prospectively over a period of 12 weeks with intermittent observation at 6 weeks also. The endpoint for analysis i.e. 3-month visit provided a clinically meaningful time frame for the demonstration of differential metabolic effects. Literature also suggest that most of the metabolic parameters appear by 4 to 12 weeks and plateau by 1 year.[13,14]

None of the patient, treated with olanzapine, developed MS at 6 weeks in the present study. Saddichha (2008) reported a prevalence of 20-25% at 6 weeks in an analysis of 99 drug naïve patients patients of first episode schizophrenia treated with olanzapine, risperidone and haloperidol.[9] Saddichha (2007) in a study found the incidence of MS (IDF criteria), which increased significantly to 31.81% at 6 weeks as compared to 3.33% at baseline.[8] This study assessing only females is good as it makes sample homogeneous but on the other hand it fails to answer how do various antipsychotics compare to each other across sex and also limits the eligibility for it results to be generalized. Moreover those patients, having MS or components of MS, at baseline were included in this study. This may have resulted in increased incidence compared to the present study, which stringently excluded such patients.

In the present study 20% patients (i.e. 6 out of 30) had MS at the end of 12 weeks with olanzapine. DeHert (2007) found MS in 24.4% with olanzapine at 3 months. The mean age of patients with all antipsychotics was

same (i.e. 33.7 years) which was comparable to mean age of present study group.[5]

Among quetiapine group 3.33% (1 out of 30) developed MS at 6 weeks and it increased to 10% (3 out of 30) at 12 weeks. We could not find any data pertaining to new onset metabolic syndrome in quetiapine at 6 weeks. DeHert (2007) found 19.1% (N=21) patients developing MS in first episode schizophrenia after 3 months of treatment with quetiapine i.e. a rate just double than what we observed in our study.[5] This difference may be because they did not include drug naïve patients as in the present study.

Although the rate of MS in the present study is lower than in other studies, it may be proposed that the findings of the present study are possibly more reliable, since the effect of single drug therapy was observed.

Limitations

- Small sample size, single sited study limited to specific region limits the generalizability of the results to the rest of Indian population.
- There was no healthy control group to compare trends of metabolic syndrome in schizophrenia to that of the general population.
- Dietary intake and activities of daily living of the patients were not taken into account, which could have helped to assess the association of lifestyle factors in metabolic syndrome.
- Investigator was not blinded to the medications prescribed. But as most of the parameters were objective observations done by investigator and moreover, laboratory technicians doing blood investigations were not aware of medication prescribed, there are least chances for the bias which could have resulted for not including blinding in the study design.

CONCLUSION

The present study confirms the emergence of metabolic syndrome and its components in schizophrenia with antipsychotic medication. The baseline metabolic parameters should be checked at baseline for all patients of schizophrenia and these results should be kept in mind before making the choice of antipsychotic treatment. Clinicians should be judicious in the use of medications with potential metabolic liabilities, to be mindful of the pattern of metabolic problems seen with antipsychotics and to routinely monitor for all metabolic syndrome criteria. Since various abnormalities of metabolic syndrome can be modified with lifestyle changes and pharmacological interventions, early detection and management of metabolic syndrome is critical to prevent complications.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Brown S. Excess mortality of schizophrenia, a meta-analysis. Br J Psychiatry. 1997;171:502-8.
2. DeHert M, Winkel R, Vaneyck D, Hanssens L, Wampers M Scheen et al. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. Schizophr Res. 2006;83:87-93.
3. Kato MM, Currier MB, Gomez CM, Hall L, Gonzalez-Blanco M. Prevalence of metabolic syndrome in Hispanic and non-Hispanic patients with schizophrenia. Primary Care Companion J Clin Psychiatry. 2004;6:74-7.
4. Zhang ZJ, Yao ZJ, Liu W, Fang Q, Reynolds GP. Effects of antipsychotics on fat deposition and changes in leptin and insulin levels. Magnetic resonance imaging study of previously untreated people with schizophrenia. Br J Psychiatry. 2004;184:58-62.
5. DeHert M, Eyck VD, Wampers M, Hanssens L, Scheen A, Peuskens J. Prevalence and incidence rates of metabolic abnormalities and diabetes in a prospective study of patients treated with second-generation antipsychotics. Schizophr Bull. 2007;33:560.
6. Perez-Iglesias R, Crespo-Facorro B, Amado JA, Garcia-Unzueta MT, Ramerez-Bonilla ML, Gonzalez-Blanch C et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. J Clin Psychiatry. 2007;68(11):1733-40.
7. DeHert M, Schreurs V, Sweers K, Eyck VD, Hanssens L, Sinko S et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: A retrospective chart review. Schizophr Res. 2008;101:295-303.
8. Saddichha S, Ameen S, Akhtar S. Incidence of new onset metabolic syndrome with atypical antipsychotics in first episode schizophrenia: a six-week prospective study in Indian female patients. Schizophr Res. 2007;95:247.
9. Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled short-term prospective study. Schizophr Res. 2008;101:266-72.
10. Perloff D, Grim C, Flack Jl. Human blood pressure determination by sphygmomanometry. Circulation. 1993;88(5):2460-70.
11. Ford ES. Prevalence of metabolic syndrome defined by the international diabetes federation among adults in the US. Diabet Care. 2005;28:2745.

12. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. Diabet Care. 2003;26:575-81.
13. Wetterling T. Bodyweight gain with atypical antipsychotics: acomparative review. Drug Safety. 2001;24:59-73.
14. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry. 2002;14:59-64.

DOI: 10.5455/2320-6012.ijrms20140538
Cite this article as: Kumar H, Gupta R, Dogra S, Joshi RK. Metabolic syndrome in schizophrenia: how much is attributable to drug treatment? Int J Res Med Sci 2014;2:569-74.