

Comparison of fasting blood sugar and serum lipid profile changes after treatment with atypical antipsychotics olanzapine and risperidone

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INTRODUCTION This study aimed to compare the effects of the two most commonly prescribed atypical antipsychotics, olanzapine and risperidone, on fasting blood sugar and serum lipid profile of the recipients.

METHODS A randomised, comparative, open clinical study was conducted on 60 schizophrenic patients. The patients were divided into two groups, one receiving olanzapine and the other receiving risperidone. The patients were assessed for changes in fasting blood sugar and serum lipid profile (triglycerides [TG], high-density lipoprotein [HDL], low-density lipoprotein [LDL], very-low-density lipoprotein [VLDL] and total cholesterol) eight weeks after starting treatment. The number of patients positive for fasting blood sugar and lipid profile criteria of metabolic syndrome was calculated by applying the modified National Cholesterol Education Programme Adult Treatment Panel III guidelines (NCEP ATP III) criteria at eight weeks.

RESULTS Patients treated with olanzapine showed a highly significant increase in the observed parameters, whereas those treated with risperidone showed a significant increase in fasting blood sugar, HDL and LDL levels, and a highly significant increase in other parameters. Intergroup comparison was insignificant except for TG, VLDL and total cholesterol levels. More men as compared to women fulfilled the NCEP ATP III criteria for metabolic syndrome in both groups.

CONCLUSION Olanzapine has a higher propensity to cause derangement of some parameters of lipid profile than risperidone. These parameters include TG, VLDL and total cholesterol levels.

Keywords: hyperlipidaemia, metabolic syndrome, olanzapine, risperidone
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INTRODUCTION

Novel atypical antipsychotics used for the treatment of schizophrenia offer significant advantages over conventional compounds, particularly because they are associated with fewer extrapyramidal symptoms than conventional antipsychotics.⁽¹⁾ However, atypical antipsychotic agents have their own drawbacks, as they may be associated with a worsening of cardiovascular risk factors such as weight gain, hyperglycaemia and hyperlipidaemia. Elevated blood pressure has been reported in patients, along with weight gain due to antipsychotic use. This is collectively known as metabolic syndrome.⁽²⁾ The health implications of metabolic syndrome as a result of long-term therapy with atypical antipsychotics may be more dangerous than the extrapyramidal syndrome typically associated with older antipsychotic agents.^(3,4)

Adiposity is the most important correlate of insulin resistance and metabolic syndrome.⁽⁵⁾ Waist circumference and body mass index (BMI) both predict the occurrence of diabetes mellitus (DM), but waist circumference is a stronger predictor of DM than BMI.^(6,7) Insulin resistance is associated with an atherogenic plasma lipid profile (elevated low-density lipoprotein [LDL] cholesterol, high plasma triglycerides [TG], elevated very-

low-density lipoprotein [VLDL] cholesterol concentration and decreased high-density lipoprotein [HDL] cholesterol concentration).^(8,9) There is a linear association between plasma triglyceride levels and coronary heart disease risk. Increasing level of plasma TG is often associated with accumulation of remnant lipoproteins, typically characterised by a high ratio of cholesterol to TG. The remnants consist of partially lipolysed VLDL, intermediate-density lipoproteins (IDL) and chylomicrons. These lipoproteins, along with LDL cholesterol, can induce foam cell formation once they are internalised by 'scavenger' receptors located on the surface of macrophages.⁽¹⁰⁾ These processes facilitate plaque formation. Low HDL cholesterol level could be an important risk factor for coronary heart disease or it could worsen the risk in the presence of other risk factors. A low level of HDL cholesterol could be pro-atherogenic and appears to be directly related to metabolic syndrome.⁽¹¹⁾

Out of all the parameters of serum lipid profile, TG and HDL levels are considered to be most important, and thus they constitute important criteria of metabolic syndrome, according to the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines. Equally important are fasting blood sugar level, waist circumference

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and blood pressure.⁽¹²⁾ In this study, we compared the effects of two antipsychotics, olanzapine and risperidone, on blood sugar levels and serum lipid profile.

METHODS

This was a prospective, randomised, comparative, open clinical study conducted by the Departments of Pharmacology and Psychiatry, Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, India, in 60 patients. A simple, standard technique for random assignment with a table of random numbers was used to allocate the treatment schedule. The patients in each group were found to be comparable at the time of their initial visit with regard to demographic parameters such as age, gender, height and weight, and other parameters like blood pressure and waist circumference. The severity of schizophrenia was also assessed and compared at the same time using the Brief Psychiatric Rating Scale.

A total of 60 patients of both genders aged 16–40 years were divided in two groups of 30 patients each. The patients were randomly allocated to receive any of two different treatments. Informed consent was obtained from the attendants of all patients enrolled for the study. Inclusion criteria were a current diagnosis of International Classification of Diseases (ICD)-10 schizophrenia, schizophreniform disorder or schizo-affective disorder. The following were the exclusion criteria: patients suffering from substance-induced psychotic disorder, psychotic disorder due to general condition or mental retardation, medical conditions known to affect the brain, any medical condition requiring treatment with a medication with psychotropic effects; medical contraindications to treatment with olanzapine or risperidone; significant risk of suicidal or homicidal behaviour; pregnant or lactating women; patients already suffering from hypertension, DM, hyperlipidaemia or obesity at the time of starting treatment with antipsychotic drugs; and a history of allergy to the study medications.

One group of patients (n = 30) received treatment with 5 mg daily oral olanzapine (Oleanz, Sirius Pharmaceuticals, Sikkim, India), and the second group (n = 30) received 2 mg daily oral risperidone (Sizodon, Symbiosis Pharmaceuticals, Sikkim, India). The doses were kept stable throughout the eight-week treatment period. The available commercial preparations were used and patient compliance was checked by interviewing the patient at every visit. The patients' baseline fasting blood sugar and lipid profile were assessed before the treatment was initiated, and at four and eight weeks of the treatment. Total serum TG, HDL, LDL, VLDL, total cholesterol and fasting blood glucose levels of the patients were recorded in a standardised format. The lipid profile and blood sugar criteria for metabolic syndrome (according to NCEP ATP III guidelines) are deemed to be met if serum HDL is < 40 mg/dL in males and < 50 mg/dL in females; serum TG is > 150 mg/dL and fasting blood sugar level > 110 mg/dL in both the genders. The number

Table I. Characteristics of study population.

Baseline parameter	Mean ± SEM	
	Olanzapine-treated (n = 30)	Risperidone-treated (n = 30)
Age (yrs)	29.20 ± 1.36	29.46 ± 1.41
Female:male*	16:14	16:14
Height (cm)	164.36 ± 1.68	164.63 ± 1.63
Weight (kg)	58.03 ± 1.80	58.33 ± 1.53
Waist circumference (cm)	77.56 ± 0.96	78.76 ± 1.00
Systolic blood pressure (mmHg)	119.4 ± 0.248	117.93 ± 0.87
Diastolic blood pressure (mmHg)	78.2 ± 0.70	79.20 ± 0.56
BPRS score	42.2 ± 0.97	43.2 ± 1.07

*Data is expressed as number of patients.

BPRS: Brief Psychiatric Rating Scale; SEM: standard error of mean

of patients meeting these criteria was analysed and compared at eight weeks.

At week zero, the homogeneity of the treatment groups for age, fasting blood sugar and lipid profile parameters was analysed using unpaired *t*-test. Mean and standard error of mean (SEM) of the readings were calculated at baseline and at four and eight weeks. Paired *t*-test was applied for intragroup analysis at different periods of the study and independent *t*-test was applied for intergroup analysis of various parameters at the end of the study. The number of patients meeting the fasting blood sugar and serum lipid profile criteria of metabolic syndrome was compared by applying the chi-square test. P-values < 0.05 and < 0.001 were considered to be significant and highly significant, respectively.

RESULTS

The baseline characteristics of the patients are tabulated in Table I. Tables II and III show the mean blood sugar, TG, HDL, LDL, VLDL and total cholesterol levels of the olanzapine- and risperidone-treated patients, respectively, at different time periods in the study. The mean increase in the blood sugar level at the end of the study period was 4.4 ± 1.97 mg/dL and 2.2 ± 0.69 mg/dL in the olanzapine and risperidone group, respectively. Despite the higher values in the group treated with olanzapine, the difference in intergroup comparison was not significant (p = 0.892 at four weeks, p = 0.502 at eight weeks). At four weeks, none of the patient from either group fulfilled the fasting blood sugar criterion for metabolic syndrome. At eight weeks, 12.5% of females and 14.28% of males treated with olanzapine fulfilled this criterion, while in the risperidone-treated group, none of the females and 7.14% of males met this criterion. No significant difference could be found in the number of patients fulfilling this criterion in the two treatment groups at the end of eight weeks.

The mean change in the values of TG over eight weeks was 30.03 ± 2.18 mg/dL and 13.23 ± 2.56 mg/dL in the olanzapine

Table II. Assessment of fasting blood sugar and serum lipid profile in the olanzapine-treated group.

Parameter (mg/dL)	Mean \pm SEM			p-value*
	Baseline	4 weeks	8 weeks	
Fasting blood sugar	85.53 \pm 1.31	87.43 \pm 1.61	89.93 \pm 1.97	< 0.001
Triglycerides	102.90 \pm 3.09	118.43 \pm 3.59	133.26 \pm 4.38	< 0.001
High-density lipoprotein	51.53 \pm 0.75	49.66 \pm 0.95	48.33 \pm 1.33	< 0.05
Low-density lipoprotein	108.43 \pm 1.98	113.06 \pm 2.03	116.66 \pm 2.93	NS
Very-low-density lipoprotein	20.50 \pm 0.62	23.63 \pm 0.72	26.56 \pm 0.88	< 0.001
Total cholesterol	180.46 \pm 2.03	186.36 \pm 2.17	193.00 \pm 2.58	< 0.001

*Comparison at 4 weeks vs. 8 weeks. $p < 0.05$: statistically significant; $p < 0.001$: highly significant; SEM: standard error of mean; NS: not significant. The differences in values at baseline vs. 4 weeks and at baseline vs. 8 weeks were highly significant for all parameters ($p < 0.001$).

Table III. Assessment of fasting blood sugar and serum lipid profile in risperidone-treated patients.

Parameter (mg/dL)	Mean \pm SEM			p-value*
	Baseline	4 weeks	8 weeks	
Fasting blood sugar	86.13 \pm 1.03	87.16 \pm 1.11	88.33 \pm 1.31	< 0.05
Triglycerides	99.66 \pm 2.55	106.76 \pm 3.57	112.90 \pm 4.70	< 0.001
High-density lipoprotein	50.10 \pm 0.74	49.30 \pm 0.90	48.56 \pm 1.02	< 0.05
Low-density lipoprotein	107.23 \pm 2.77	108.53 \pm 3.05	111.80 \pm 3.26	< 0.05
Very-low-density lipoprotein	19.93 \pm 0.51	21.33 \pm 0.70	22.56 \pm 0.94	< 0.001
Total cholesterol	177.30 \pm 2.59	179.26 \pm 2.70	181.53 \pm 2.93	< 0.001

*Comparison at 4 weeks vs. 8 weeks. $p < 0.05$: statistically significant; $p < 0.001$: highly significant; SEM: standard error of mean. Differences in the fasting blood sugar, HDL and LDL were statistically significant, while those in TG, VLDL and total cholesterol were highly significant at baseline vs. 4 weeks and at baseline vs. 8 weeks.

and risperidone groups, respectively. On intergroup comparison, significant difference in the values was seen at eight weeks only ($p = 0.025$ and $p = 0.002$ at four and eight weeks, respectively). Numerically higher values were seen in olanzapine-treated patients. Only 3.33% of men in the olanzapine group and none of the patients in the risperidone group fulfilled the TG criterion for metabolic syndrome at four weeks. 31.25% of females and 50% of males from the olanzapine group fulfilled this criterion at eight weeks. In the risperidone-treated group, 12.5% of females and 28.57% of males met this criterion at eight weeks. Despite the higher percentage of patients who met this criterion in the olanzapine group, this difference was not statistically significant at the end of the study period.

The mean decline in HDL values at the end of eight weeks was 3.20 ± 0.74 mg/dL and 1.2 ± 0.43 mg/dL in the olanzapine and risperidone groups, respectively. However, when the values were compared within the different treatment groups, no significant differences were seen at any point of the study ($p = 0.782$ and $p = 0.890$ at four and eight weeks, respectively), although the values were numerically lower in the olanzapine group. 10% of females and 6.66% of males in the olanzapine group and 3.33% of females and 6.66% of males in the risperidone group fulfilled the HDL criterion for metabolic syndrome at four weeks. At eight weeks, 25% of females and 35.71% of males in the olanzapine group met this criterion. Among the risperidone-treated patients, this criterion was met by 12.5% of females and 21.42% of males. Despite the higher number of olanzapine-treated patients fulfilling this criterion, no statistically significant intergroup difference could be found at the end of the study period.

The mean increase in LDL values at the end of the study period was 8.23 ± 2.09 mg/dL and 4.66 ± 1.41 mg/dL in the olanzapine and risperidone groups, respectively. Although the LDL level was numerically higher in olanzapine-treated patients, this difference was not statistically significant ($p = 0.221$ at four weeks and $p = 0.331$ at eight weeks).

The mean change in VLDL values over eight weeks was 6.06 ± 0.428 mg/dL and 2.56 ± 0.49 mg/dL in the olanzapine and risperidone groups, respectively. Although there was no statistical difference between the groups at four weeks ($p = 0.027$), the VLDL levels were significantly higher ($p = 0.003$) in the olanzapine-treated patients than those treated with risperidone at the end of eight weeks. The mean increase in total cholesterol at the end of the study period was 12.53 ± 1.43 mg/dL and 4.63 ± 0.52 mg/dL in the olanzapine and risperidone groups, respectively. The mean total cholesterol levels were significantly higher in the olanzapine-treated group, as revealed on intergroup comparison at four and eight weeks ($p = 0.01$ and $p = 0.005$ at four and eight weeks, respectively).

DISCUSSION

The natural course of the onset of DM secondary to antipsychotic drugs is not well understood, although there are several proposed mechanisms to explain its occurrence. One possibility is the disruption of glucose transport into peripheral tissues. It has been suggested that antipsychotic drugs may block glucose accumulation directly at the level of the glucose transporter (GLUT) protein in both the peripheral and brain tissue, leading to hyperglycaemia.^(13,14) It has also been postulated that the blockade of 5HT_{2A} receptor may suppress glucose

uptake in skeletal muscle.⁽¹⁵⁾ Another possibility is a derangement of pancreatic function, more specifically beta cell function, in the presence of newer atypical antipsychotics.^(13,14) The blockade of muscarinic type 3 (M_3) and 5-HT_{1A} receptors is thought to be the reason behind diminished pancreatic beta cell responsiveness.⁽¹⁵⁾ Excess body fat is also a very important factor that leads to insulin resistance, and this is in turn responsible for metabolic syndrome.⁽⁵⁾ There is a strong independent relationship between visceral and subcutaneous adiposity and insulin resistance.⁽¹⁶⁾ When adipocyte storage capacity is exceeded, there is an overflow and accumulation of free fatty acids in the form of toxic ceramide, long chain fatty acyl-CoA and sphingolipid in the muscle, liver, pancreas and arteries.^(17,18) Accumulation of fat within the liver and muscle leads to insulin resistance in these tissues, resulting in elevated fasting plasma glucose levels (due to accelerated hepatic glucose production) and postprandial hyperglycaemia (due to decreased insulin-mediated glucose uptake by the muscle). Insulin becomes elevated with obesity, as higher insulin levels are necessary to send glucose into the cells, and thus the beta cells in the pancreas become exhausted, increasing the risk of DM.^(19,20)

Insulin resistance is also seen to be associated with an atherogenic plasma lipid profile.^(8,9) Some antipsychotic medications may impair and/or alter the action of insulin on adipocytes, leading to progressive lipid accumulation.⁽²¹⁾ The impaired effect of insulin on adipocytes may partly explain weight gain-independent dyslipidaemia.^(22,23) The combination of augmented VLDL synthesis (secondary to hyperinsulinaemia of insulin resistance) and impaired VLDL removal (secondary to diminished insulin action on lipoprotein lipase) causes a net increase in plasma VLDL and TG, and ultimately, LDL cholesterol. The defect in lipoprotein lipase activity also contributes to the decrease in plasma HDL cholesterol observed in insulin-resistant states.⁽²⁴⁾ The reason behind the different propensity of olanzapine and risperidone to cause derangement of the lipid profile and elevated blood glucose is not properly understood, but it may be due to different affinities of the drugs to attach to the various receptors.

A study conducted by Sikich et al reported a non-significant increase in values of fasting blood sugar in both olanzapine- and risperidone-treated patients after eight weeks of treatment. The increase was numerically greater in olanzapine-treated patients.⁽²⁵⁾ The findings of the current study are similar to those of Sikich et al. Similar results have also been reported by Lindenmayer et al and McEvoy et al.^(26,27) Some other long-duration studies also reported similar differences in fasting blood sugar elevations in olanzapine- and risperidone-treated groups.^(28,29) Another study conducted by Sikich et al on a different group of patients revealed contradictory results, in which patients treated with risperidone were found to have a greater increase in fasting blood sugar values compared to olanzapine-treated patients.⁽³⁰⁾

Sikich et al's 2004 study reported a non-significant decrease of HDL levels in olanzapine-treated patients after eight weeks

and slightly increased HDL levels in risperidone-treated patients. LDL and TG levels were also increased in both groups.⁽²⁵⁾ The 2008 study conducted by Sikich et al on a different group of patients, however, showed different results, with a slight increase in HDL levels in olanzapine-treated patients and a decrease in HDL levels in risperidone-treated patients after eight weeks of treatment. LDL levels showed a slight increase in olanzapine-treated patients, but they decreased in risperidone-treated patients. TG levels were found to be increased in both the groups, while total cholesterol levels were increased in olanzapine-treated patients but decreased in risperidone-treated patients.⁽³⁰⁾ Mc Evoy et al's study showed decrease in HDL levels but a rise in TG and total cholesterol levels in both olanzapine- and risperidone-treated patients after 12 weeks of treatment. The change was numerically higher in the olanzapine-treated patients.⁽²⁷⁾ Our findings are in accordance with the findings of previous studies. Lindenmayer et al reported an increase of baseline total cholesterol levels after 14 weeks of both olanzapine and risperidone treatment in their study, but the rise was statistically significant only in the olanzapine-treated group.⁽²⁶⁾ A cross-sectional study conducted by McCormack and Wiseman revealed no significant differences in LDL levels in olanzapine- and risperidone-treated individuals.⁽³¹⁾ Some other long-duration studies also revealed more gain in TG and total cholesterol levels in the olanzapine group as compared to the risperidone group.^(28,29) Another cross-sectional study conducted by Henderson et al demonstrated no significant differences in total cholesterol levels attained after olanzapine and risperidone treatment.⁽³²⁾

Certain discrepancies have been observed in the findings of the current study and those of previous studies. This could be due to the differences in study populations in terms of ethnic and genetic characteristics, baseline values, age groups and dosing schedules used (some studies used an escalating dosing schedule). Moreover, there is also a difference in the tendency for changes in the lipid profile and blood glucose parameters among different population groups. This study is not without its limitations. First, no placebo control was used in view of the ethical problems; instead, a comparison was made using an active control only. Furthermore, the study measured the adverse effects of the drugs for only a short period of time (the study duration was eight weeks), and the number of patients in each group was also relatively small.

In conclusion, this study compared the effects of olanzapine and risperidone on three important parameters of metabolic syndrome, namely fasting blood glucose, TG and HDL. In addition to these parameters, other components of lipid profile have also been compared for additional information. Both drugs have been seen to affect these parameters, but the change in values was found to be numerically greater with olanzapine as compared to risperidone. However, on intergroup comparison, statistically significant difference was seen only for three parameters – TG, VLDL and total cholesterol. The values were

higher in the olanzapine-treated group. Thus, it can be concluded that olanzapine has a greater propensity to cause derangement of some parameters of lipid profile compared to risperidone.

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