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Diabetes and schizophrenia – effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia

Saddichha S, Manjunatha N, Ameen S, Akhtar S. Diabetes and schizophrenia – effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia.

Objective: There have been innumerable advances in the pharmacotherapy of schizophrenia, but problems have emerged hand-in-glove, such as the presence of treatment-emergent glucose intolerance and frank diabetes mellitus (DM).
Method: Medication-naïve patients with schizophrenia ($n = 99$) underwent baseline fasting and 2 h post-prandial plasma glucose measurements repeated after 6 weeks after randomization to receive olanzapine, risperidone or haloperidol. The results were compared with a matched healthy control group.
Results: A significant difference ($P = 0.002$) in baseline 2 h post-prandial blood sugar (PPBS) was noted between the control group and the treatment group along with a significant increase in weight ($P < 0.001$), fasting blood sugar ($P = 0.01$) and 2 h PPBS ($P < 0.001$) from baseline to endpoint between the groups. A statistical significance in the incidence of DM at endpoint by the WHO criteria (10.1%) was also noted.
Conclusion: Male patients with schizophrenia are liable to develop DM. Antipsychotic treatment leads to the development of DM in a significant 10.1% within 6 weeks.

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Key words: diabetes; first-episode psychosis; schizophrenia; antipsychotics; olanzapine; risperidone; haloperidol

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Significant outcomes

- Patients treated with antipsychotics are at a higher risk of developing glucose intolerance. This is in addition to the increased risk that the disease process itself confers on these patients.

Limitations

- The single-centre nature of our study and findings on an ethnic population limit the generalizability.
- The study did not control for herbal treatments prior to start of the study.

Introduction

Atypical antipsychotics form the first-line management of schizophrenia today, yet studies have pointed to their complicity in developing disturbances in glucose intolerance and frank diabetes mellitus (DM). Several comprehensive reviews have concluded that atypical antipsychotics have a significantly increased risk of new-onset DM compared to conventional antipsychotics, which may or may not be dependent on development of adiposity (1–6). However, dissenting opinions are also present. Bottai et al. (7) were unable to definitely conclude that treatment with atypical or conventional antipsychotics increased risk of treatment-emergent diabetes as data were both

insufficient as well as conflicting. Haddad (8) also concluded that retrospective studies cannot reliably quantify this association, as they do not adequately control for confounding risk factors for diabetes, and suggested that well-designed prospective studies, which account for potential confounders, are needed to investigate the true association between antipsychotic medications and diabetes.

There is, however, some evidence suggesting that individuals with schizophrenia may have additional risk due to the disease of schizophrenia itself. High rates of medical mortality and increased risk of morbidity have been associated with schizophrenia (9, 10). Patients with mental illness have been observed to have an increased risk of developing diabetes, regardless of antipsychotic use (11–15). Several researchers believe that schizophrenia may be a significant and independent risk factor for both diabetes and impaired glucose tolerance (16–18). Some argue that the etiology may be genetic (19), others argue that stress, particularly dysfunction of the hypothalamo-pituitary axis (HPA) axis may be responsible (20) and yet others argue that the unhealthy diets, sedentary lifestyles and substance use in patients with schizophrenia may be responsible for glucose disturbances (21).

Unfortunately, the existing evidence has several methodological limitations. These include the limited number of randomized controlled trials, the cross-sectional or retrospective design in most studies which precludes causal relationships to be identified, effect of other medications that can cause glucose intolerance such as antidepressants (22) and mood stabilizers (23) and presence of other confounders such as prior antipsychotic treatment and the impact of baseline weight. Such limitations can be overcome by prospective studies on first-episode schizophrenic patients, who being drug naïve, avoid the confounding effect of prior antipsychotic treatment (8). Further, randomization minimizes the effects of potential confounders and reduces bias. To date, there have been only five such studies.

Sowell et al. (24) collected and grouped together the prospectively collected random blood glucose test data from a series of 5013 patients who participated in 24 randomized controlled trials (RCTs) comparing olanzapine, haloperidol, risperidone and clozapine. They reported an overall incidence rate of glucose abnormalities of 1.9% for the whole group, using a random glucose value of ≥11.1 mmol/l anytime after baseline. However, they failed to individualize the risk for each drug. Lindenmayer et al. (25) found an incidence of abnormally high blood glucose levels of 14% (14/101) in a follow-up period of only 14 weeks. Fasting blood glucose levels >6.9 mmol/l were used as the standard definition of diabetes, and patients with existing diabetes were excluded from the study. Unfortunately the findings of this study could not be generalized as the sample involved patients with treatment-resistant schizophrenia and the medication dosages used were higher compared to normal prescribing practice. The FDA study (26) reported rates of glycemic abnormalities to be similar between aripiprazole (4.7%) and olanzapine (4.5%) cohorts. No association was also found between weight gain and blood glucose abnormalities. All the above studies again had another obvious methodological limitation, that of either lack of a control group (drug free or a placebo-treated control) or using subjects who had already been exposed to antipsychotics. The only prospective study of first-episode schizophrenia comes from a 12-month RCT in which 160 patients in China were randomized to treatment with clozapine or chlorpromazine (27). Fasting blood glucose levels were tested at 3-month intervals after baseline assessment. No treatment difference was seen between the patient groups, and no incident case of diabetes was reported. However, there was a mild rise in fasting blood glucose levels noted at 52 weeks compared to baseline, with no between-group difference.

In the clinical antipsychotic trials in intervention effectiveness (CATIE) study, the largest prospective study performed on the effectiveness of antipsychotic drugs, (28), blood glucose was elevated the most with olanzapine (by 15.0 ± 2.8 mg/dl), somewhat with quetiapine (by 6.8 ± 2.5 mg/dl), risperidone (by 6.7 ± 2.0 mg/dl), and perphenazine (by 5.2 ± 2.0 mg/dl), and not more than trivially with ziprasidone (by 2.3 ± 3.9 mg/dl). Glycosylated hemoglobin (HbA1C) was elevated with olanzapine (by 0.41 ± 0.09 mg/dl), but not with the other agents (ranging from −0.10 to +0.08). There was however no comparison with a well-matched control group.

Aims of the study

To investigate the effects of antipsychotics, olanzapine, risperidone and haloperidol on fasting and 2 h post-prandial plasma glucose and development of diabetes in a drug-naïve population and compared it with a matched healthy control group. We also aimed to assess whether these differences were present in the baseline, rendering those afflicted by schizophrenia susceptible to developing diabetes.

Material and methods

All consecutive patients with a DSM-IV diagnosis of schizophrenia, in the Central Institute of Psychiatry, Ranchi, India which is a referral psychiatric institute, were asked to participate in an extensive screening and prospective follow-up study of fasting and post-prandial glucose, after obtaining written informed consent as per the guidelines of the Institutional Review Board for Biomedical Research. The prospective inclusions started in June 2006 and patients were followed up for a period of 6 weeks until December 2006.

Patients with other psychiatric comorbidity, history of severe physical illness, alcohol and substance abuse or dependence and history of pre-existing diabetes or hypertension or family history of hypertension or DM were excluded from the study at the initial screening. All patients were drug-naïve on admission; however, we did not evaluate for herbal treatments as visits to faith healers, before psychiatric consultation, is very common in India. Patients included in the study were randomized to receive risperidone, olanzapine or haloperidol. No other drugs, which could potentially influence the glucose levels, were allowed for the observation period. All patients received the same diet and underwent the same daily regimen (as in-patients) therefore controlling for these confounding variables. A healthy control group matched in terms of gender, age, exercise and diet (by basal metabolic rate) (29) and other confounding variables such as socioeconomic status, education and race was also chosen from consecutively seen accompanying persons of patients attending the institute. This control group belonged to similar educational, socioeconomic and residential backgrounds as the patients.

The baseline screening consisted of fasting and 2 h post-prandial oral glucose tolerance test (OGTT) using 75 g glucose and weight recording using standard weighing machine. For the OGTT, the patients were instructed to fast overnight and were observed by a nurse both on the night rounds and during the OGTT, in order to insure the reliability of test results. These measurements were repeated at 6 weeks (endpoint). All assessments were performed by a single investigator blind to the diagnosis and medication prescribed and all investigations were carried out in the same laboratory. We used two definitions of DM, which was defined as fasting glucose level > 125 mg/dl and/or a 2-h post-glucose load > 199 mg/dl, according to ADA (30) or as fasting glucose level > 109 mg/dl and/or a 2-h post glucose load > 199 mg/dl, according to WHO (31).

This study was performed in accordance with the broad framework of the Declaration of Helsinki (32) and was approved by the institutional ethical committee.

Statistical analysis

Descriptive statistics were computed for clinical variables and the differences across the time-line were assessed by a multivariate repeated-measures test. The development of diabetes defined either by ADA or WHO was assessed using the chi-squared test.

The sample size of the present study was 99 of which 66 (66.7%) were diagnosed as suffering from paranoid schizophrenia and 33 (33.3%) from undifferentiated schizophrenia. The mean duration of untreated illness was 20.5 ± 18.5 months. The mean age of the subjects was 26.06 ± 5.57 years. Further, 35 (35.4 %) of the subjects were on stable dosages of olanzapine (mean dosage of 16.5 ± 4.6 mg), 33 (33.3 %) were on risperidone (mean dosage of 4.4 ± 1.2 mg) and 31 (31.3%) were on haloperidol (mean dosage of 13.4 ± 3.6 mg).

Results

Table 1 presents the comparison of sociodemographic and other baseline measurements between the study group and the control group. There were no significant differences between the groups in age, gender and fasting blood sugar (FBS), when it

Table 1. Baseline comparison of control and treatment groups

Variables	Control group (n = 51)	Treatment group-combined (n = 99)	t-Test/χ^2	df	P-value
Age (in years)					
All	27.5 ± 5.9	26.0 ± 5.5	1.491	148	0.138
Male	26.8 ± 4.1	25.6 ± 4.8	1.103	80	0.273
Female	28.5 ± 7.9	26.4 ± 6.3	1.131	66	0.262
Gender					
Male	30 (58.8%)	52 (52.5%)	0.539	1	0.493
Female	21 (41.2%)	47 (47.5%)			
Education (in years)	9.7 ± 4.4	10.7 ± 4.3	1.413	148	0.160
Weight (kg)					
All	50.4 ± 4.3	48.5 ± 9.5	1.325	148	0.188
Male	52.0 ± 2.3	52.4 ± 9.4	0.235	80	0.814
Female	48.0 ± 5.2	45.3 ± 7.6	2.005	66	0.05
Fasting blood sugar					
All	80.8 ± 6.3	82.2 ± 10.7	0.898	148	0.371
Male	80.3 ± 6.7	81.0 ± 11.1	0.102	80	0.729
Female	81.5 ± 5.7	83.6 ± 10.3	0.859	66	2.066
Post-prandial blood sugar					
All	90.9 ± 7.9	95.6 ± 12.3	2.433	148	0.016*
Male	90.4 ± 8.3	97.4 ± 13.9	2.521	80	0.014*
Female	91.7 ± 7.4	93.5 ± 10.1	0.733	66	0.466

*Significance at $P < 0.05$.

Table 2. Comparison of weight and serum glucose from baseline to endpoint between various groups

	Weight (kg)			FBS (mg/dl)			PPBS (mg/dl)		
	Baseline	Endpoint	F (df = 3)	Baseline	Endpoint	F (df = 3)	Baseline	Endpoint	F (df = 3)
Control									
All (n = 51)	50.3 (4.3)	50.4 (4.2)	44.1*	80.8 (6.3)	80.8 (6.3)	3.8†	90.9 (7.9)	89.4 (6.9)	12.6*
Male (n = 30)	52.0 (2.3)	52.0 (2.0)	39.9*	80.3 (6.7)	80.3 (6.7)	3.37‡	90.4 (8.3)	88.4 (7.3)	8.89*
Female (n = 21)	48.0 (5.3)	48.0 (5.3)	13.0*	81.5 (5.7)	81.5 (5.8)	1.33	91.7 (7.4)	90.8 (6.2)	5.0§
Olanzapine									
All (n = 35)	47.0 (11.5)	52.0 (11.6)		81.7 (10.8)	88.3 (18.0)		96.8 (14.5)	118.4 (40.4)	
Male (n = 18)	52.5 (12.5)	57.7 (12.9)		79.7 (11.6)	89.4 (22.2)		100.6 (16.9)	129.8 (51.8)	
Female (n = 17)	41.1 (6.6)	46.0 (5.7)		83.9 (9.6)	87.2 (12.8)		92.7 (10.4)	106.2 (17.9)	
Risperidone									
All (n = 33)	49.0 (9.6)	53.2 (9.7)		83.9 (11.8)	88.2 (11.3)		94.1 (9.9)	115.1 (24.8)	
Male (n = 18)	52.0 (9.3)	55.7 (9.2)		83.1 (12.4)	90.2 (12.1)		94.7 (10.3)	121.7 (27.3)	
Female (n = 15)	45.5 (9.0)	50.2 (9.6)		84.8 (11.5)	85.7 (10.1)		93.4 (9.7)	107.1 (19.4)	
Haloperidol									
All (n = 31)	49.8 (6.5)	52.2 (6.4)		81.1 (9.5)	88.0 (15.4)		95.8 (12.3)	102.6 (14.7)	
Male (n = 16)	52.9 (4.9)	55.1 (4.9)		80.3 (9.0)	88.1 (16.8)		97.0 (13.7)	103.6 (17.3)	
Female (n = 15)	46.5 (6.4)	49.1 (6.4)		82.0 (10.2)	87.8 (14.4)		94.6 (10.9)	101.6 (11.4)	

Values are expressed as mean (SD).
*Significance at 0.001 level.
†Significance at 0.01 level.
‡Significance at 0.023 level.
§Significance at 0.004 level.

Table 3. Comparison of diabetes by ADA and WHO criteria between various groups

Variables	Control group (n = 51)	Treatment group-olanzapine (n = 35)	Treatment group-risperidone (n = 33)	Treatment group-haloperidol (n = 31)	Treatment group-combined (n = 99)	Chi-squared (patients vs. control)	P-value
Diabetes by ADA criteria							
All	0 (0.0)	1 (2.9)	0 (0.0)	1 (3.2)	2 (2.0)	1.044	0.548
Male	0 (0.0)	1 (5.6)	0 (0.0)	1 (6.3)	2 (3.8)	1.183	0.530
Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Diabetes by WHO criteria							
All	0 (0.0)	4 (11.4)	3 (9.1)	3 (9.7)	10 (10.1)	5.519	0.016*
Male	0 (0.0)	2 (11.1)	2 (11.1)	2 (12.5)	06 (11.5)	3.735	0.081
Female	0 (0.0)	2 (11.8)	1 (6.7)	1 (6.7)	04 (8.5)	1.899	0.303

Values within parenthesis are expressed in percentage.
*Significance at $P < 0.05$.

was analyzed for the whole group or divided into males and females. However, a significant difference ($P = 0.002$) in 2 h post-prandial blood sugar (PPBS) was noted between the control group and the treatment group, which persisted only for males ($P = 0.001$).

Table 2 presents the comparison of different variables from baseline to endpoint across all groups. Multivariate analysis was performed between the three treatment groups (olanzapine, risperidone and haloperidol) and the control group. There was a statistically significant increase in weight ($P < 0.001$), FBS ($P = 0.01$) and 2 h PPBS ($P < 0.001$) from baseline to endpoint between the groups. This significance persisted when the data were analyzed across genders. However, there was no significant difference in FBS among females.

When the incidence of DM at endpoint (Table 3), between treatment and control groups was analyzed, a statistical significance by the WHO criteria (10.1%, $P = 0.016$; $\chi^2 = 5.51$) was noted which was however not reflected by the ADA criteria (2%, $P = 0.5$; $\chi^2 = 1.04$). Further, the incidence of diabetes by WHO criteria was noted only among males ($P = 0.05$; $\chi^2 = 3.73$) but not among females.

Among the FBS measurements, the olanzapine group gained the maximum of mean 6.6 (±12.7) mg/dl followed by risperidone at 4.3 (±12.5) mg/dl and haloperidol at 6.8 (±14.1) mg/dl. The olanzapine group also gained the maximum in PPBS of mean 21.5 (±32.2) mg/dl followed by risperidone at 21.0 (±23.4) mg/dl and haloperidol at 6.7 (±12.6) mg/dl. Male subjects appeared to gain more in all parameters than females: FBS –

8.2 (± 14.3) mg/dl compared to 3.2 (± 10.9) mg/dl for females and PPBS – 21.5 (± 31.0) mg/dl compared to 11.4 (± 15.2) mg/dl for females.

Treatment-emergent diabetes was present in 11.4% of subjects in the olanzapine group, 9.1% of subjects in the risperidone group and 9.7% of subjects in the haloperidol group by WHO definition and in 2.9% of subjects in the olanzapine group, 3.2% of subjects in the haloperidol group and none in the risperidone group by ADA definition.

Discussion

Schizophrenia is an illness which has attracted the most attention during the recent decade due to its increased medical morbidity and mortality when compared with the general population (9, 10). There has been increased recognition that the advent of modern pharmacotherapy, especially atypical antipsychotics, is associated with adverse effects on weight and other metabolic parameters (2–6).

Our study on the incidence of treatment-emergent DM in drug-naïve patients diagnosed with schizophrenia is the largest study on an Indian population to date. It has attempted to answer many of the questions that previous studies threw up by its prospective design and has controlled for confounding variables by both matching and randomization. We have also attempted to answer the oft-repeated question of schizophrenia itself being associated with glucose intolerance by comparing a drug-naïve population with a matched control group. We chose the 6-week period as it represents an often followed time frame in clinical practice to determine treatment outcome and decide on treatment discontinuation.

The results of this study reveal that patients with schizophrenia, especially male patients, may be inclined to have glycemic abnormalities prior to the initiation of any antipsychotic treatment (at baseline), which has been corroborated by another small study in this population (18). This liability to develop future diabetes has been hypothesized to be due to HPA axis dysfunction leading to raised cortisol levels and hence development of insulin resistance and DM (33). Such a finding may indicate that schizophrenia itself confers a higher risk on individuals in terms of metabolic profile (34, 35).

However, the diabetogenic role of antipsychotics is also demonstrated with an incidence of treatment-emergent diabetes within 6 weeks of treatment with antipsychotics, either typical or atypical, by both WHO criteria (10.1%) and ADA criteria (2.0%) when compared with the control group. The rise in both FBS and PPBS levels, at endpoint, in the treated group compared to the control group, further bolsters this argument.

Among antipsychotics, olanzapine seems to have the most diabetogenic potential causing a mean increase in both FBS (6.6 mg/dl) and PPBS (21.5 mg/dl) when measured from baseline to endpoint. Risperidone follows, with treatment causing a mean increase of 4.3 and 21 mg/dl, respectively. Haloperidol comparatively fares better, but not too much, causing a mean increase of 6.8 and 6.7 mg/dl. These findings are similar to that of the CATIE study and the several reviews carried out (1–6). In addition to olanzapine and risperidone, our findings seem to indicate that haloperidol also has a similar role to play in the development of metabolic complications.

Among subjects divided by gender, an increase in glucose profile is even more obvious in male subjects as they gained a mean 8.2 mg/dl (FBS) and 21.5 mg/dl (PPBS) compared to females who gained a mean 3.2 and 11.4 mg/dl, between baseline and endpoint. Further, males also appeared to develop DM at higher rates than females when compared to the control group. Combined with the apparent glucose intolerance at baseline, male subjects appear to be predisposed to developing DM on antipsychotics, contrary to other studies (36) reporting glucose abnormalities more among females (30.5%) than males (22.6%). However, in similar studies from this subcontinent, male patients have considerably fared worse in measures of cholesterol, glucose or obesity (37, 38). On the whole, increases in both FBS and PPBS is a matter of grave concern as Indians are particularly sensitive to gaining weight around the waist and developing DM as well as other cardiovascular diseases (39).

We have shown that patients with schizophrenia may have an increased risk of developing glycemic abnormalities, which is accelerated by the administration of antipsychotics, both typical and atypical. The implications for treatment are to develop treatment for specific risk groups. Greater caution and intensive screening along with targeting of specific risk factors is the need of the hour. Clinicians should consider switching patients to a medication that is less likely to cause disturbances in glucose regulation before development of clinical DM. Treatment needs of patients should be individualized keeping in view the risk–benefit ratio and possible future consequences.

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