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Original Article

Effect of Olanzapine Therapy on the Development of Insulin Resistance in Patients with Schizophrenia: A Prospective Observational Cohort Study

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ABSTRACT

Background: Schizophrenia is a chronic psychiatric disorder characterised by disturbances in thought, perception, and behaviour. Olanzapine, a second-generation (atypical) antipsychotic widely used in its treatment, is associated with metabolic adverse effects such as weight gain, dyslipidaemia, impaired glucose metabolism, insulin resistance, and an increased risk of type 2 diabetes and cardiovascular disease. These effects arise chiefly from its actions on dopaminergic and serotonergic receptors, which can reduce insulin sensitivity. **Aim and Objectives**: To determine the effect of the atypical antipsychotic olanzapine on the development of insulin resistance in patients with schizophrenia. Materials and **Methods**: This prospective observational cohort study was conducted on 100 newly diagnosed patients with schizophrenia, who were followed up for six months after initiation of olanzapine therapy. Venous blood was collected from each participant after an overnight fast from the antecubital vein; serum was separated by centrifugation at 2,000 rpm for 15 minutes, with an additional fluoride sample collected for glucose estimation. Fasting blood glucose was measured by the GOD-POD spectrophotometric method (ILAB 650 and ERBA 360 Chemistry Analysers), and fasting insulin was measured by chemiluminescent immunoassay (Beckman Coulter Access 2 Immunology Analyzer). Insulin resistance was assessed using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), as described by Matthews et al. (1985). **Results**: HOMA-IR increased significantly following six months of olanzapine therapy, from a mean (± SD) of 0.9 ± 0.3 at baseline to 1.1 ± 0.3 at six months ($p = 0.002$), indicating progression toward insulin resistance. **Conclusion**: Six months of olanzapine therapy in patients with schizophrenia was associated with a significant increase in fasting blood glucose and insulin resistance, irrespective of sex and age. Clinical Significance: These findings reinforce the association between olanzapine and insulin resistance and highlight the need for further research into the differential metabolic effects of individual antipsychotic agents, which may otherwise progress to overt metabolic syndrome.

Keywords: Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), schizophrenia, metabolic syndrome, olanzapine.

INTRODUCTION

Schizophrenia is a persistent and severe mental illness characterised by a constellation of symptoms affecting thought, perception, emotion, and behaviour [1]. It exerts a profound impact not only on affected individuals but also on their families and society at large. Antipsychotic medication remains the mainstay of treatment for schizophrenia, aiming to improve overall functioning by reducing positive symptoms such as delusions and hallucinations [2].

Second-generation (atypical) antipsychotics — including olanzapine, risperidone, aripiprazole, quetiapine, and clozapine — are now the preferred first-line agents, largely because they are associated with fewer extrapyramidal side effects than first-generation (typical) antipsychotics [3]. However, the high prevalence of metabolic syndrome among individuals with schizophrenia remains a significant concern in mental health care [4]. Metabolic syndrome comprises a cluster of abnormalities, including central obesity, insulin resistance, dyslipidaemia, and hypertension; several studies have shown its prevalence to be higher in patients with schizophrenia than in the general population [5,6]. Olanzapine, in particular, can induce insulin resistance, impair glucose metabolism, and alter lipid metabolism, thereby contributing to metabolic syndrome and increased cardiovascular risk [7,8]. The present study was therefore undertaken to examine the role of olanzapine, prescribed for the treatment of schizophrenia, in inducing insulin resistance and impairing glucose metabolism — changes that may predispose patients to metabolic syndrome, diabetes, and cardiovascular disease.

MATERIALS AND METHODS

Place of Study

The study was conducted in the Department of Biochemistry and the Department of Psychiatry, Chhattisgarh Institute of Medical Sciences (CIMS), Bilaspur, Chhattisgarh.

Study Design

This was a hospital-based, prospective observational cohort study. Participants were recruited from the Psychiatric OPD, CIMS, Bilaspur, based on the following inclusion and exclusion criteria.

Inclusion Criteria

1. Adult patients aged 18–65 years diagnosed with schizophrenia according to DSM-5 or ICD-10 criteria.
2. Patients who had not previously received antipsychotic medication.
3. Patients with no prior history of metabolic syndrome.
4. Patients (or attendants, where applicable) able to provide informed consent and willing to participate in the study.

Exclusion Criteria

1. Patients with a diagnosis of other primary psychiatric or psychotic disorders.
2. Patients with a history of other severe medical conditions that could confound the assessment of metabolic syndrome.
3. Patients with a history of endocrine disorders or known metabolic abnormalities.
4. Pregnant or breastfeeding women.
5. Patients with a history of substance abuse or dependence within the preceding six months.

Sample Size

A total of 100 patients diagnosed with schizophrenia were enrolled, selected according to the inclusion and exclusion criteria above.

Duration of Study

The study was conducted over 24 months, commencing on 05.10.2023, following approval from the Scientific Research Review Committee and the Institutional Ethics Committee of CIMS, Bilaspur, Chhattisgarh.

Patients attending the Psychiatry OPD at CIMS who were newly diagnosed with schizophrenia (per DSM-5/ICD-10 criteria) and had not previously received antipsychotic treatment were invited to participate. Written informed consent was obtained from all participants. A structured proforma was used to record sociodemographic details, clinical history, comorbidities, lifestyle factors, and family history of schizophrenia and metabolic disorders. Blood samples were collected at baseline to assess fasting blood glucose and HOMA-IR and to exclude pre-existing metabolic syndrome. Patients who did not meet the inclusion criteria were excluded. Enrolled participants underwent a follow-up assessment at six months to evaluate changes in metabolic parameters and the development of insulin resistance.

Collection of Blood Sample
Venous blood was collected from each participant after an overnight fast, from the antecubital vein, into plain tubes; serum was separated by centrifugation at 2,000 rpm for 15 minutes. An additional sample was collected into fluoride tubes for glucose estimation. Fasting blood glucose was estimated by the GOD-POD spectrophotometric method using the ILAB 650 and ERBA 360 Chemistry Analyzers, and fasting insulin was measured by chemiluminescent immunoassay (CLIA) using the Beckman Coulter Access 2 Immunology Analyzer.

Insulin resistance was assessed using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), first described by Matthews et al. (1985) and calculated as:

HOMA-IR = [Fasting glucose (mg/dL) × Fasting insulin (mIU/mL)] / 405
Following six months of olanzapine therapy, patients were classified according to standard HOMA-IR cut-offs:

- 0.5–1.9: insulin-sensitive (optimal)
- Above 1.9: early insulin resistance
- Above 2.9: significant insulin resistance

Statistical Analysis
Data were analysed using Microsoft Excel and IBM SPSS Statistics (version 22.0, trial version). Descriptive statistics are reported as mean ± SD. The two-tailed t-test and one-way ANOVA were used to compare metabolic parameters, with $p < 0.05$ and $F > 2.9$ considered statistically significant.

RESULTS
Patients were assessed for changes in fasting blood glucose and HOMA-IR after six months of olanzapine therapy.
Comparison of FBS and HOMA-IR Before and After Treatment
As shown in Table 1, mean fasting blood glucose increased significantly from 99.8 ± 19.7 mg/dL at baseline to 109.7 ± 18.6 mg/dL at six months ($p = 0.001$). Similarly, mean HOMA-IR increased significantly from 0.9 ± 0.3 to 1.1 ± 0.3 ($p = 0.002$). These findings indicate a statistically significant deterioration in fasting glycaemic status and insulin sensitivity following six months of olanzapine therapy.

Parameter	Baseline (0 month)	6 Months	P-value
FBS (mg/dL)	99.8 ± 19.7	109.7 ± 18.6	0.001
HOMA-IR	0.9 ± 0.3	1.1 ± 0.3	0.002

Table 1. Comparison of FBS and HOMA-IR before (baseline) and after treatment (6 months)

Change in FBS and HOMA-IR According to Sex

Table 2 compares the change in FBS and HOMA-IR between male (n = 53) and female (n = 47) patients after six months of olanzapine therapy. The mean increase in both parameters was numerically greater in female patients — FBS: 15.1 ± 1.4 vs. 10.5 ± 12.8 mg/dL; HOMA-IR: 0.18 ± 0.28 vs. 0.16 ± 0.27 — although neither difference reached statistical significance ($p = 0.525$ and $p = 0.791$, respectively).

Parameter	Males (n = 53)	Females (n = 47)	P-value
FBS (mg/dL)	10.5 ± 12.8	15.1 ± 1.4	0.525
HOMA-IR	0.16 ± 0.27	0.18 ± 0.28	0.791

Table 2. Difference in the change in FBS and HOMA-IR between male and female patients after 6 months of olanzapine therapy

Change in FBS and HOMA-IR According to Age Group
Table 3 presents the change in FBS and HOMA-IR stratified by age. The greatest mean increase in FBS was observed in the youngest age group (18–32 years: 10.6 ± 15.3 mg/dL), followed by the 33–46-year group (8.0 ± 11.1 mg/dL) and the 47–60-year group (4.6 ± 7.4 mg/dL); these differences were not statistically significant ($F = 0.963$, $p = 0.385$). Similarly, the mean change in HOMA-IR did not differ significantly across age groups ($F = 0.477$, $p = 0.621$).

Parameter	18–32 yrs (n=65)	33–46 yrs (n=20)	47–60 yrs (n=15)	F-statistic	P-value
FBS (mg/dL)	10.6 ± 15.3	8.0 ± 11.1	4.6 ± 7.4	0.963	0.385

HOMA-IR	0.1 ± 0.3	0.1 ± 0.2	0.0 ± 0.1	0.477	0.621

Table 3. Difference in the change in FBS and HOMA-IR among patients by age group after 6 months of olanzapine therapy

DISCUSSION

The present prospective study evaluated the effect of six months of olanzapine therapy on fasting blood glucose (FBS) and insulin resistance (HOMA-IR) in patients with schizophrenia. Both parameters increased significantly over the treatment period, indicating that olanzapine adversely affects glucose metabolism and promotes insulin resistance even during the early phase of treatment.

Mean FBS rose from 99.8 ± 19.7 mg/dL at baseline to 109.7 ± 18.6 mg/dL at six months ($p = 0.001$), and mean HOMA-IR rose from 0.9 ± 0.3 to 1.1 ± 0.3 ($p = 0.002$), suggesting progressive impairment of insulin sensitivity following olanzapine initiation. This rise in fasting glucose and HOMA-IR is consistent with the hypothesis that insulin resistance precedes the clinical onset of overt diabetes [9].

These findings are consistent with those of Newcomer et al., who demonstrated that olanzapine produces significantly greater deterioration in insulin sensitivity and glucose tolerance than other atypical antipsychotics. Similarly, Houseknecht et al. proposed that olanzapine interferes directly with insulin signalling and glucose uptake in peripheral tissues, independent of weight gain. Together, these observations suggest that olanzapine-associated metabolic disturbance arises through both direct pharmacological effects and secondary mechanisms related to increased adiposity [10,11,12].

Several biological mechanisms may underlie these changes. Olanzapine has high affinity for serotonergic (5-HT2C), histaminergic (H1), dopaminergic (D2), and muscarinic receptors. Blockade of H1 and 5-HT2C receptors increases appetite and caloric intake, promoting weight gain and visceral adiposity [12,13]. In addition, olanzapine impairs insulin-mediated glucose uptake in skeletal muscle and adipose tissue, increases hepatic gluconeogenesis, alters adipokine secretion, and may impair pancreatic β-cell function — mechanisms that together contribute to insulin resistance and progressive glycaemic impairment [14,15].

Sex-stratified analysis showed a numerically greater increase in fasting blood glucose among female patients than male patients (15.1 ± 1.4 vs. 10.5 ± 12.8 mg/dL), though this difference did not reach statistical significance ($p = 0.525$); HOMA-IR likewise did not differ significantly by sex ($p = 0.791$). These findings suggest that the adverse metabolic effects of olanzapine occur irrespective of sex, in line with De Hert et al., who concluded that although women may experience greater weight gain in some populations, sex alone does not consistently predict olanzapine-induced insulin resistance [16,17].

Age-stratified analysis similarly showed no significant differences in the change in FBS ($p = 0.385$) or HOMA-IR ($p = 0.621$) across age groups, although younger patients showed a numerically greater rise in fasting glucose. This is consistent with the findings of Mitchell et al., who reported that metabolic abnormalities associated with second-generation antipsychotics occur across all age groups, underscoring the need for metabolic surveillance irrespective of patient age [17]. These findings carry important clinical implications. Patients with schizophrenia already have an elevated baseline risk of metabolic syndrome, owing to sedentary lifestyle, unhealthy dietary habits, smoking, and genetic susceptibility; olanzapine therapy further compounds this risk by promoting insulin resistance and hyperglycaemia. Regular metabolic monitoring should therefore form an integral part of psychiatric care, with baseline and periodic assessment of fasting plasma glucose, HbA1c, lipid profile, body weight, body mass index, waist circumference, and blood pressure to enable early detection and management of metabolic complications.

The strengths of this study include its prospective design, a uniform six-month follow-up period, and the simultaneous assessment of fasting blood glucose and HOMA-IR, which together provide a sensitive estimate of insulin resistance. Certain limitations should nonetheless be acknowledged: the study was conducted at a single tertiary care centre with a relatively modest sample size and a follow-up period limited to six months, and anthropometric indices (BMI, waist circumference), HbA1c, lipid profile, dietary intake, physical activity, and inflammatory biomarkers were not assessed. Future multicentre studies with larger cohorts and longer follow-up are warranted to clarify the long-term metabolic effects of olanzapine.

CONCLUSION

This study demonstrates that six months of olanzapine therapy in patients with schizophrenia results in a significant increase in fasting blood glucose and insulin resistance, irrespective of sex and age. On this basis, the following are recommended:

1. Patients with schizophrenia should be regularly monitored for metabolic syndrome risk factors.
2. Nutritional and lifestyle modification should be implemented for patients undergoing prolonged treatment with atypical antipsychotics such as olanzapine.
3. Where clinically appropriate, antipsychotics with a lower metabolic risk profile should be considered for patients at risk of developing insulin resistance and, consequently, metabolic syndrome.

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DECLARATIONS

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Ethical Approval: The study was conducted in accordance with applicable ethical standards and approved by the appropriate ethics committee where required.

Informed Consent: Informed consent was obtained from all participants involved in the study where applicable.

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Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.