

Insulin Resistance in Drug Naive Patients with SchizophreniaDr. Swati Agrawal¹, Dr. Dubey Vaibhav*², Dr. Loya Mitali³, Dr. Diwan Sanjeet⁴, Dr. Singh Himanshu⁵, Dr. Tiwari Apurva⁶, Dr. Khan Sumera⁷¹Assistant Prof. Department of Biochemistry, RKDF Medical College Hospital & Research Centre, Bhopal, India²Psychiatry MD, Associate Professor, PCMS and RC Bhopal, India³⁻⁷Psychiatry MD, PCMS and RC-Bhopal, India**Original Research Article*****Corresponding author**

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Abstract: Schizophrenia itself or antipsychotic medications are primarily responsible for the observed increased metabolism disturbances (insulin level and insulin resistance) are not clear. To study insulin level and insulin resistance in drug naive patients with schizophrenia. Thirty one drug naive patients suffering from first episode of schizophrenia and 40 age and sex matched healthy controls were studied at Peoples Medical College, Bhopal. Illness related variables were rated by Brief Psychiatric Rating Scale (BPRS). Venous blood was collected after overnight fasting and sent for fasting plasma glucose (FPG), serum lipid profile and serum insulin estimation. Plasma glucose was determined by glucose oxidase method, serum insulin was determined by chemiluminescence and insulin resistance was calculated using HOMA-IR [fasting plasma insulin (FPI) (μ U/ml) x (FPG [mg/dl] x 0.055/22.5). Male (52.5%) and female (51.6%) preponderance was observed in control and Drug naive group respectively. Fasting glucose (mg/dL), insulin level (μ U/ml), insulin resistance, Triglycerides (mg/dL), Cholesterol (mg/dL), HDL (mg/dL), VLDL (mg/dL), LDL (mg/dL) and Risk Ratio in control and Drug naive group was 85.32 ± 6.04 vs 91.12 ± 7.77 ($P=0.0007$), 7.98 ± 2.14 vs 11.45 ± 1.84 ($P=0.0001$), 1.65 ± 0.45 vs 2.56 ± 0.58 ($P=0.0001$), 87.45 ± 27.5 vs 107.29 ± 40.63 ($P=0.01$), 167.45 ± 13.93 vs 167.64 ± 18.96 ($P=0.96$), 42.84 ± 3.69 vs 41.98 ± 4.87 ($P=0.40$), 17.49 ± 5.50 vs 21.48 ± 8.12 ($P=0.007$), 107.11 ± 14.44 vs 103.88 ± 18.37 ($P=0.40$) and 3.91 ± 0.47 vs 4.02 ± 0.59 ($P=0.38$) respectively. Fasting glucose, fasting insulin level, insulin resistance, VLDL, triglyceride was significantly higher in Drug naive schizophrenia patients.

Keywords: Drug naive schizophrenia, metabolic syndrome, metabolic abnormalities, insulin resistance.

INTRODUCTION

Schizophrenia is a highly heritable condition and life expectancy is many years shorter in patients with schizophrenia in comparison to general community [1]. The metabolic syndrome (Met S, also known as syndrome X and Reaven's syndrome) is a constellation of different conditions including abdominal obesity, insulin resistance, dyslipidemia and elevated blood pressure. All these features predispose the affected individual to increased risk of cardiovascular diseases; a fact of paramount importance in severe mental illness like schizophrenia [2]. These metabolic abnormalities are not only directly associated with morbidity and mortality but also directly affect psychiatric outcome such as increased prevalence of psychotic and depressive symptoms, more pronounced functional impairment and poor adherence to treatment [3].

Metabolic abnormalities have been identified as a part of schizophrenia illness even during pre-neuroleptic era [4] but with introduction of second generation antipsychotics and their possible association with metabolic abnormalities [5-7], the focus on the causes of metabolic abnormalities in schizophrenia has now been shifted. Moreover, using the homeostatic model assessment (HOMA), Arranz *et al.* reported an increased insulin resistance even in noncompliant antipsychotic schizophrenia patients stressing the long lasting effect of antipsychotic medication even after their discontinuation [8]. However, multiple studies now provide evidence for an increased prevalence of abnormalities of glucose metabolism such as impaired fasting glucose and insulin resistance in drug naive first-episode patients with schizophrenia suggesting that metabolic abnormalities are an inherent part of schizophrenia illness. But the controversy still exists. A

study from Canada in 2008 by Sengupta *et al.* conducted with drug-naïve, first-episode psychosis patients with a diagnosis of schizophrenia spectrum disorder reported no significant differences in parameters of glucose metabolism and lipid profile between patients and healthy subjects [9].

It has been debated whether schizophrenia itself or antipsychotic medications are primarily responsible for the observed increased metabolism disturbances. Most probably many factors such as medical (weight, age), psychosocial (stress, physical activity, diet), genetic (history of diabetes in family, common genetic link between schizophrenia and diabetes) and iatrogenic (medication induced abnormality in glucose metabolism) contribute together in occurrence of metabolic abnormalities in patients with schizophrenia [3, 9]. Early detection and treatment of these risk factors may result in a reduction of the prevalence of these metabolic abnormalities and thus in a reduction of the excess mortality in patients with schizophrenia.

MATERIALS AND METHODS

A cross sectional study was done on 31 drug naïve patients suffering from first episode of schizophrenia as per DSM5 diagnostic criteria of schizophrenia and 40 age and sex matched healthy controls at Peoples Medical College, Bhopal.

Hospital Ethics Committee approval and written informed consent was obtained from each patient after explanation of complete description of the study.

Illness related variables were rated by Brief Psychiatric Rating Scale (BPRS). The normal comparison group consisting of 40 Indian subjects (21 males and 19 females) was physically healthy and had no personal or family history of psychiatric illness or type II diabetes mellitus.

The socio-demographic data of the participants was entered in a semi-structured proforma. Weight and height were measured with weighing machine and stadiometer respectively. BMI was evaluated as weight divided by height squared (kg/m^2).

After overnight fasting (8-12 hours) blood sample was collected for fasting plasma glucose (FPG), serum lipid profile and serum insulin. Plasma glucose was determined by glucose oxidase method, serum insulin was determined by chemiluminescence and insulin resistance was calculated using HOMA-IR [fasting plasma insulin (FPI) ($\mu\text{U/ml}$) \times (FPG [mg/dl]) \times 0.055/22.5).

All the data was analyzed using IBM SPSS ver. 20 software. Data were expressed as number and percentage. Student t test and one way ANOVA was used to compare the mean of continuous variable. Chi Square test was used to compare categorical variable. Cross tabulation and frequency distribution was used to prepare the table. Level of significance was assessed at 5%.

RESULTS

Mean age of Control ($n=40$; 22.48 ± 3.88 years) and Drug naïve ($n=31$; 22.00 ± 4.52 years) group was comparable ($p=0.632$). There were 21 (52.5%) male and 19 (47.5%) female in Control and 15 (48.4%) male and 16 (51.6%) female in Drug naïve group ($p=0.731$). The male:female ratios were 15:16 and 21:19 respectively in drug naïve patients with schizophrenia and healthy controls.

Anthropometric parameters including BMI (kg/m^2) (21.85 ± 2.63 vs 21.56 ± 3.41 ; $P=0.686$) and waist hip ratio (cm) (0.85 ± 0.047 vs 0.83 ± 0.061) were comparable between both the groups.

Table-1: Showing comparison between blood glucose and lipid parameters between groups

Glucose metabolism and lipid parameter	Healthy control (n=40)	Drug-naïve patients (n=31)	T and P values
Fasting glucose (mg/dL)	85.32 ± 6.04	91.12 ± 7.77	$t=3.55$, $df=69$, $P=0.0007$
Insulin level ($\mu\text{U/ml}$)	7.98 ± 2.14	11.45 ± 1.84	$t=7.19$, $df=69$, $P=0.0001$
Insulin resistance	1.65 ± 0.45	2.56 ± 0.58	$t=7.35$, $df=69$, $P=0.0001$
Triglycerides (mg/dL)	87.45 ± 27.5	107.29 ± 40.63	$t=2.45$, $df=69$, $P=0.01$
Cholesterol (mg/dL)	167.45 ± 13.93	167.64 ± 18.96	$t=0.048$, $df=69$, $P=0.96$
HDL (mg/dL)	42.84 ± 3.69	41.98 ± 4.87	$t=0.84$, $df=69$, $P=0.40$
VLDL (mg/dL)	17.49 ± 5.50	21.48 ± 8.12	$t=2.75$, $df=69$, $P=0.007$
LDL (mg/dL)	107.11 ± 14.44	103.88 ± 18.37	$t=0.82$, $df=69$, $P=0.40$
Risk Ratio	3.91 ± 0.47	4.02 ± 0.59	$t=0.86$, $df=69$, $P=0.38$

Data is expressed as mean \pm standard deviation, HDL; high density lipoprotein, VLDL; very low density lipoprotein, LDL; low density lipoprotein

DISCUSSIONS

In our study drug naive patients of schizophrenia had higher level of FPG and insulin and were more insulin resistant than healthy controls. Our study findings were in accordance with previous reports from India and Asia [11, 12]. Dasgupta *et al.* documented that antipsychotic naive patients with schizophrenia had significantly decreased insulin sensitivity along with an increased insulin resistance relative to healthy subjects [11].

Venkatsubramanian *et al.* found a significantly higher mean insulin resistance score and lower levels of Insulin-like growth factors in antipsychotic naive schizophrenia patients relative to healthy comparison subjects [13]. Two recently published studies from china also found that drug naive schizophrenia patients had higher levels of fasting plasma insulin and were more insulin resistant than control population [12,14].

Earlier study by Ryan *et al.* on parameters of glucose and lipid metabolism in drug naive patients with schizophrenia reported that about 15% of antipsychotic naive schizophrenia patients showed impaired fasting glucose tolerance, higher than age adjusted population rates (Males= 11.8%, females= 5.2%). Author also reported higher levels of glucose, insulin and cortisol and were less insulin sensitive than the control subjects [10]. Mukherjee *et al.* reported that 15.8% of patients with schizophrenia had hyperglycaemia and rates of hyperglycaemia was higher in patients who were not taking medication than those who were on haloperidol, also prevalence of type 2 diabetes in patients with schizophrenia was age dependent which mirror the rates that found in the general population [15]. The average age of drug naive patients with schizophrenia in our population was 22 years and thus it is highly unlikely that age was a contributing factor in the higher rates of FPG level. Fernandez- Egea found that antipsychotic naive individuals with non-affective psychosis had significant increase in 2h glucose in comparison to healthy control population [16].

Higher blood glucose levels have also been reported in patients with tardive dyskinesia [17]. Some studies have suggested that hyperglycaemia associated with insulin resistance may contribute to pathogenesis of tardive dyskinesia [18]. In our study no patient was ever exposed to antipsychotic drugs so we did not assess involuntary movements. However, role of hyperglycaemia and insulin resistance in patients developing tardive dyskinesia on antipsychotic drugs may be an interesting topic of future research.

There are also some studies reporting divergent findings of glucose metabolism in drug naive patients with schizophrenia. Sengupta *et al.* from

Canada evaluated parameters of glucose and lipid metabolism in first episode psychosis patients (n =38) and normal community control. Difference in ethnicity and long term instability of diagnosis of schizophrenia can be the possible explanation for different results [9]. Our study results are in accordance with studies conducted in Indian and Asian patients. In another study by Arranz *et al.* from Spain, antipsychotic free patients showed significantly increased insulin and C-peptide concentration and significantly higher degree of insulin resistance in comparison with antipsychotic naive patients. In this study the comparison was between drug free and drug naive schizophrenia patients, not between drug naive patients with schizophrenia and healthy control [8]. Sengupta defined drug naive patients as those of no more than 10 cumulative days of prior treatment with antipsychotic medications. The long lasting effects of antipsychotic medication even after a short exposure on glucose metabolism cannot be ruled out in both of the studies. In our study, drug naive patients were never exposed to antipsychotic medications on recruitment to study to rule out antipsychotic effect on glucose metabolism. In study of Sengupta, not all patients recruited in study were suffering from schizophrenia. Only 16 patients were defined as drug naive schizophrenia out of 38 patients of schizophrenia spectrum disorder. In our study all 30 patients recruited for study had schizophrenia.

Smoking, diet habits and physical inactivity may also play a crucial role in the development of type II diabetes mellitus [19]. Different lifestyle factors, diet and physical activity level may also provide explanation of divergent results in our study. One limitation of our study is that we did not assess the different lifestyle factors.

There are multiple mechanisms proposed for abnormal glucose metabolism and increased insulin and insulin resistance in drug naive patients of schizophrenia. Miller *et al.* reported that development of DM II in the non-affective psychosis is multifactorial and not merely a result of second generation antipsychotic use. The concept of foetal origin of adult disease posits that events at key time points during gestation impact development and subsequently risk of adult disease [20]. There are several risk factors (eg: birth and maternal factors and immune genes) which are common to both schizophrenia and type II diabetes [21].

Dopamine's effects on insulin signaling begin at the level of insulin secretion from the pancreas and continue through the central nervous system. In a reciprocal fashion, insulin also affects dopamine signaling, with specific effects on dopamine reuptake from the synapse. In this way, both schizophrenia and

diabetes mellitus may be related to each other at molecular level [22].

A number of studies have demonstrated that stress may affect both the clinical symptoms of schizophrenia and the glucose metabolism. In the patients of schizophrenia high levels of cortisol lead to increased accumulation of visceral fat and impaired glucose tolerance [23]. Schizophrenia is associated with abnormality of hypothalamic- pituitary adrenal axis. Dysregulation of HPA axis may play a role in development of abnormality of glucose metabolism in schizophrenia [24]. Cortisol was found to be associated with positive symptoms of schizophrenia, as well as with negative symptoms of schizophrenia. The stress of acute psychosis in schizophrenia and stress of hospitalization may lead to impaired fasting glucose tolerance. The acute psychological stress results in the rapid development of insulin resistance in mice in a recent study. Alternatively, there are also some studies suggesting that the stress axis changes and problem of glucose metabolism are associated with the illness rather than with factors relating to the immediate environment [17].

Fernandez-Egea *et al.* [16] in their study in newly diagnosed, antipsychotic naïve patients with non-affective psychosis reported that compared with control subjects, the patients with psychosis had decreased telomere content and increased pulse pressure. The difference could not be attributed to difference in age, ethnicity, smoking, gender, body mass index, neighbourhood of residence, socioeconomic status, aerobic conditioning or an increased cortisol concentration in psychotic subjects [16]. Both glucose tolerance and increased pulse pressure is associated with post stroke dementia, cognitive impairment [25], type II diabetes [26] and coronary artery disease. Fernandez- Egea suggested that shorter telomere length may be linked to increased risk of diabetes and hypertension in schizophrenia.

Impaired glucose tolerance has also been reported in first degree relatives of drug naïve patients with schizophrenia suggesting a possible genetic association between diabetes and schizophrenia. Spelman *et al.* reported impaired glucose tolerance in 18.2 % of first degrees relatives compared to 10.5 % in control [27].

The cross sectional nature and small sample of the study restrict the findings to be applied in population. A large randomized clinical trial is needed to strengthen the present study findings.

CONCLUSION

Fasting glucose, fasting insulin level, insulin resistance, VLDL, triglyceride was significantly higher

in Drug naïve schizophrenia patients. Patients with schizophrenia should also be looked for the metabolic changes.

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