

Level of Insulin Resistance in Schizophrenia Patients and Its Association with Treatment with Antipsychotics

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Abstract

Background: Abnormalities in glucose metabolism were noticed in schizophrenia patients even before the era of antipsychotics. Studies have also found development of new onset diabetes mellitus in patients treated with antipsychotics. The current study was conducted to assess insulin resistance in schizophrenia patients receiving typical or atypical antipsychotics, as well as, those who were not taking any antipsychotic drug.

Method: In this cross sectional study, conducted in a tertiary referral centre, 120 male patients with diagnosis of Schizophrenia, Schizotypal and Delusional disorders (ICD-10 DCR), were divided into three groups: those who were receiving typical antipsychotic (haloperidol, chlorpromazine) (N=37), those who were receiving atypical antipsychotic (olanzapine, clozapine, risperidone) (N=43) and those who were not receiving any antipsychotic (N=40) for a period of at least three months preceding the study. Patients were assessed for fasting plasma glucose, fasting serum insulin and the level of insulin resistance.

Results: Patients in the groups receiving antipsychotics (typical or atypical) were found to have higher level of insulin resistance and fasting serum insulin in comparison to those not receiving any antipsychotic (p=0.009). The mean value was highest in those treated with risperidone. However, the difference in fasting glucose was not significant.

Conclusion: Both typical and atypical antipsychotics are associated with higher level of insulin resistance and certain atypical agents are implicated more than other antipsychotics.

Keywords: Schizophrenia; Antipsychotic; Level of insulin resistance

Introduction

Speculation of disturbances in glucose metabolism in schizophrenia could be dated as far back as Henry Maudsley [1]. The first report of abnormality in glucose regulation in schizophrenia dates back prior to the introduction of antipsychotic medication [2]. These early reports suggested that patients with psychotic disorders might have some elevated baseline risk for glucoregulatory disturbances, prior to any consideration of adverse side effects of antipsychotics. Phenothiazine treatment was observed to contribute to abnormalities in glucose regulation including reports of aggravation of existing diabetes and new onset diabetes mellitus [3-5]. After introduction of newer antipsychotic agents, there were reports of associated hyperglycemia, exacerbation of existing type 1 and type 2 diabetes mellitus, new onset type 2 diabetes mellitus with clozapine, olanzapine and risperidone [6-8]. Subsequently, lots of studies came up with varying results. One of the proposed mechanisms for development of diabetes mellitus (type 2) has been insulin resistance, where the target organs for insulin become less sensitive, or resistant, to insulin. So even in normal concentration of insulin in serum there is subnormal biological response for this hormone.

In 2005, Henderson et al. [9] studied schizophrenia patients cross-sectionally for glucose metabolism, who were on atypical antipsychotics. But in their study, there was no control group, no group on typical antipsychotics and they used only stable patients. So, there was no way to compare these three populations. In 2002, Newcomer et al. [10] concluded from their study that antipsychotic treatment of non-diabetic patients with schizophrenia can be associated with adverse effect on glucose regulation. But this study had a potential bias by using healthy controls. Also they didn't test for insulin resistance, thus giving no clue about the mode of development of diabetes

mellitus. In a longitudinal study spanning over 60 months, Henderson et al., observed the relation of clozapine with diabetes mellitus, weight gain and lipid abnormalities [9]. But absence of a control group was a serious limitation. In a significant study, effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid abnormalities in 1st episode schizophrenia were studied [11]. But they failed to incorporate widely used typical antipsychotics like haloperidol and chlorpromazine in their study. Absence of control group was also a limitation.

The current study was conducted with efforts to overcome those limitations and intended to assess insulin resistance in schizophrenia patients receiving typical or atypical antipsychotics, as well as, those who were not taking any antipsychotic drug.

Method

This was a cross-sectional, naturalistic study, conducted in a tertiary referral centre. Data were collected using purposive sampling technique with International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Diagnostic Criteria for Research (ICD-10 DCR) [12] as the guide for diagnosis. The study got

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approval from the institutional review board. Outpatients and long stay male inpatients, aged 18-60 years, diagnosed as Schizophrenia, Schizotypal and Delusional Disorder (ICD-10 DCR) [12] were taken up for the study after obtaining informed consent from subjects. The total number of patients taken up in the current study was 120. The study population was divided into three groups: those who were receiving single typical antipsychotic (haloperidol, chlorpromazine) (N=37), those who were receiving single atypical antipsychotic (olanzapine, clozapine, risperidone) (N=43) and those who were not receiving any antipsychotic (N=40) for a period of at least three months preceding the study. Patients with current substance abuse/dependence, existing diabetes mellitus (or a positive family history), on medications known to affect glucose metabolism (steroids, beta-blockers, prolonged use of non-steroidal anti-inflammatory drugs, thiazide diuretics, sodium valproate, etc.) and patients on more than one antipsychotics were excluded from the current study.

Socio-demographic data were noted. Then blood samples were collected from the patients to estimate fasting plasma glucose, serum insulin and level of insulin resistance, which were then compared across the three study groups. Fasting plasma glucose was estimated by Glucose Oxidase Peroxidase method, by Olympus analyzer (Olympus Optical Co. Ltd, Shizuoka-ken, Japan). Fasting serum insulin was estimated through Micro particle Enzyme Immunoassay, by insulin kit (BioSource INS-EASIA Kit, Catalogue number KAP1251, manufactured by BioSource Europe S.A., Rue de l'Industrie, 8, B-1400 Nivelles, Belgium). Level of insulin resistance was calculated by using Homeostasis model of Assessment of Insulin Resistance (HOMA-IR). Homeostatic model assessment (HOMA) of β -cell function and insulin resistance (IR) was first described by Matthews et al. in 1985 [13]. After modification by Hermans et al. [14] now it is calculated by following formula:

$$[\text{Fasting serum insulin concentration} \times \text{fasting plasma glucose concentration} / 22.5]$$

The HOMA model is derived from a mathematical assessment of the interaction between β -cell function and IR in an idealized model that is then used to compute steady-state insulin and glucose concentrations. The output of the model is calibrated to give normal β -cell function of 100% and normal IR of 1. Once this interrelationship is calculated, one can estimate β -cell function and IR for any pair of

plasma glucose and insulin concentrations without having to refit the model. The HOMA and insulin values increase for insulin-resistant patients. HOMA estimates of β -cell function and insulin sensitivity are usually not normally distributed. So the data has to be logarithmically transformed and reported as geometric means with appropriate measures of dispersion [15]. HOMA has been compared with a number of well-validated methods used to measure IR and β -cell function (like the hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp) and has been found to be a useful tool for the purpose [14,15].

The authors could not find any established cut off value of HOMA for insulin resistance for Indian population. Even for the western population there are controversies regarding the cut off value, with most of the opinions varying between 1.21 and 3.16 [13,16-18]. So no such cut off value for insulin resistance was set up for the current study. The study groups were compared on the basis of the level of insulin resistance, instead.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS), 10th version, for Windows. Socio-demographic variables across three study groups were compared using Chi-square test. One way Analysis Of Variance (ANOVA) was done to compare age across the groups. Metabolic parameters were compared using one way ANOVA to analyze the data and post-hoc analysis was done using Tukey's HSD. As there were a number of drugs in each group (typical and atypical) and there was wide variation in the number of subjects on each of these drugs, Kruskal-Wallis test was done for comparing the different clinical parameters among control group and patients on individual drugs, while post-hoc analysis was done using Mann-Whitney test. It was found that data of plasma glucose, serum insulin and HOMA IR was not normally distributed. So these were transformed into logarithmic values. Later these were transformed back to exponential value. Statistically significant difference was taken at $p < 0.05$.

Results

The three study groups were comparable on socio demographic parameters (Table 1). The mean value of fasting serum insulin and level of insulin resistance were significantly lower in the control group than the groups on atypical antipsychotics and on typical antipsychotics (Table 2). However, the difference between the groups receiving typical

Variable	Off treatment (N=40) (M ± S.D) /n (%)	On Atypicals (N=43) (M ± S.D) /n (%)	On Typical (N=37) (M ± S.D) /n (%)	χ^2/F	df	p
Age (in years)	31.10 ± 9.06	35.74 ± 10.86	31.68 ± 9.60	2.716	2,117	0.070
Marital Status				2.011	2	0.366
Single	18 (45)	24 (55.8)	15 (40.5)			
Married	22 (55)	19 (44.2)	22 (59.5)			
Education				0.947	4	0.918
Illiterate	2 (5)	4 (9.3)	2 (5.4)			
≤ 10 th	25 (62.5)	24 (5.8)	23 (62.2)			
>10 th	13 (32.5)	15 (34.9)	12 (32.4)			
Occupation				0.910	2	0.634
Unemployed	21 (52.5)	27 (62.8)	21 (56.8)			
Working	19 (47.5)	16 (37.2)	16 (43.2)			
Monthly income				3.949	4	0.684
<3000	24 (60)	23 (53.5)	19 (51.4)			
3000-6000	10 (25)	9 (20.9)	8 (21.6)			
>6000	6 (15)	11 (25.6)	9 (24.3)			
Family background				3.198	2	0.202
Rural	29 (72.5)	23 (53.5)	23 (62.2)			
Urban	11 (27.5)	20 (46.5)	14 (37.8)			
Family type				4.263	2	0.119
Nuclear	10 (25)	10 (23.3)	3 (8.1)			
Joint	30 (75)	33 (76.7)	34 (91.9)			

Table 1: Comparison of socio-demographic variables among groups.

Variable	Off treatment [a] (N=40) (Mean ± S.D)	On Atypicals [b] (N=43) (Mean ± S.D)	On Typical [c] (N=37) n (%)	F (df=2,117)	p	Post-hoc (Tukey's HSD)
F P Glucose	5.64 ± 1.21	5.58 ± 1.26	5.26 ± 1.26	1.129	0.327	-
F S Insulin	7.54 ± 1.99	12.81 ± 2.03	13.60 ± 2.72	6.409	0.002*	b>a (p=0.010) c>a (p=0.005)
HOMA-IR	1.90 ± 1.99	3.42 ± 2.48	3.16 ± 3.10	4.863	0.009*	b>a (p=0.012) c>a (p=0.042)

*significant at p<0.05

HOMA-IR=Homeostasis Model Assessment of Insulin Resistance

FP Glucose=Fasting Plasma Glucose

FS Insulin=Fasting Serum Insulin

Table 2: Comparison of metabolic parameters among groups.

Variable	Kruskal-Wallis test		Post-hoc (Mann-Whitney test)
	χ ² (df=6)	p	
Fasting glucose	9.497	0.148	Off<Olz, Hpl, Rsp Off<Rsp, Olz, Hpl
Fasting Insulin	15.947	0.014*	
HOMA-IR	14.613	0.023*	

Off-Off treatment, Olz-Olanzapine, Rsp-Risperidone, Hpl-Haloperidol

Table 3: Comparison of metabolic parameters among individual drugs.

and atypical antipsychotics did not reach the threshold of significance. In non-parametric tests (Table 3) statistically significant difference was found to exist on fasting serum insulin (p=0.014) and level of insulin resistance (p=0.023). Lower value was seen in the controls in comparison to all other groups. The difference was significant between control group and those on risperidone, olanzapine or haloperidol. Those receiving risperidone had the highest mean value for HOMA IR while those on olanzapine had the highest mean value for fasting insulin.

Discussion

Selection of control group makes a notable difference between the present study and most of the other studies. Schizophrenia patients who were not receiving any medication were used as control group. This was done to control the effects of the disease itself on the above parameters, as several studies have found significant difference on those parameters between normal healthy population and schizophrenia population. Nearly equal numbers of patients were taken in each group to maintain homogeneity. The study had a naturalistic design wherein the treatment was left to the treating team. Patients having extremes of age (<18 yrs, >60 yrs) were excluded from the study to avoid biases, which are age related, on metabolic parameters. Only male patients were included and females excluded to avoid the possible bias caused by differential effect of antipsychotics on glucose metabolism in the two sexes, as observed in one recent study [18].

Henderson et al. [9] found significant difference among different groups (clozapine>olanzapine>risperidone) whereas Newcomer [10] found modest increase in HOIMA IR values in patients treated with clozapine in comparison to other agents. A recent meta-analysis in 2015 [19] has observed insulin resistance in schizophrenia to be associated more with use of clozapine, olanzapine and risperidone. As reported in literature and observed in our study, abnormality in glucose metabolism (fasting serum insulin and insulin resistance) has been found more frequently in patients of schizophrenia treated with typical or atypical antipsychotics in comparison to those who are not. Also, in current study, it was found that there was significant difference in some of those parameters between agents in the two groups of antipsychotics. May be due to difference in number of subjects on individual agents

and opposing effects on particular parameter of agents belonging to same group and similar effects of agents of different group and vice versa on certain parameters, significant difference did not surface.

There are a number of potential mechanisms for the association of atypical antipsychotic medication with hyperglycemia. Typically, insulin resistance is an early feature, which is initially compensated in part, by increased production of insulin by pancreatic cells (i.e., hyperinsulinaemia) [20]. Controlled studies have suggested treatment effects on insulin resistance, rather than a primary defect in insulin secretion [21]. Dywn et al. [22] reported effects of antipsychotic medications on glucose transporter function. Serotonin receptor activity has also been hypothesized to be involved in glucose control, with both 5-HT1a and 5-HT2 receptors implicated [7,23-26]. The fact that the present study found significant difference in HOMA IR and serum insulin level among different groups without any significant difference on fasting glucose point towards presence of insulin resistance in patients receiving certain antipsychotic agents which happens to be a risk factor for type 2 diabetes mellitus. Apart from the fact that certain agents in both groups (typical and atypical antipsychotics) can be implicated for these, certain atypical antipsychotics (olanzapine and risperidone) surpass the typical ones in this regard.

The findings of this study calls for vigilance about insulin resistance while treating patients with schizophrenia, though it is necessary to conduct further studies with designs to overcome limitations of the current study like unequal distribution of patients on different antipsychotic drugs, before generalizing the observations made here.

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