

# Beta-cell Function and Metabolic Clearance Rate of Glucose in Patients with Major Mental Health Disorders on Antipsychotic Drug Treatment

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Authors' contribution: KSA designed the study, VOL made the diagnosis, SKR did the laboratory analysis, all authors recruited the patients, SKR wrote the draft of the manuscript while all authors edited and approved of the final draft of manuscript, KSA supervised the entire research.

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**Abstract:** *Background:* Insulin resistance and metabolic alteration continue to be essential features of major mental health disorders (MMHD) with poorly understood and multifaceted mechanisms. This study was carried out to provide information on insulin resistance, beta-cell function, metabolic clearance rate of glucose and their possible interplay with duration of antipsychotic use in patients with major mental health disorders.

*Methodology:* Plasma levels of glucose and insulin were determined in 124 patients with MMHD after an overnight fast and at 30 and 120 min of standard Oral Glucose Tolerance Test. Thereafter, indices of insulin resistance, beta-cell function and estimated metabolic clearance rate of glucose (eMCR) were calculated appropriately. Statistical analysis was done using ANOVA, Kruskal Wallis, independent Student's t-test and Mann-Whitney U. P-values less than 0.05 were considered as statistically significant.

*Results:* Metabolic factors (fasting and postprandial glucose and insulin), indices of insulin sensitivity and  $\beta$ -cell function were not significantly different when patients with schizophrenia, bipolar and depression were compared with one another. Postprandial insulin level at 30 min (30 min PPI), estimated First and Second Phases of Insulin Release (eFPIR, eSPIR) were significantly lower in patients on atypical antipsychotic drugs [18.15 (3.57-40.35)  $\mu$ U/ml], 617.63 (320.06-911.31) pmol/l, 180.30 (114.82-249.39) pmol/l] compared with patients on typical antipsychotic drugs [27.48 (13.33-47.68)  $\mu$ U/ml, 767.69 (530.58-1198.35) pmol/l, 209.89 (154.01-310.97) pmol/l]. Furthermore, the mean waist circumference and body mass index were significantly higher in patients who have been on anti-psychotic drug for more than 10 years compared with patients with less than 5 years history of anti-psychotic use. eMCR of glucose progressively declined with increasing duration of antipsychotic use and it was significantly lower in patients who have been on antipsychotic drugs for more than 10 years [8.09 (5.90-9.44) ml.kg<sup>-1</sup>.min<sup>-1</sup>] compared with patients who have been on the drugs for less than 5 years [9.03 (7.47-10.04) ml.kg<sup>-1</sup>.min<sup>-1</sup>].

*Conclusion:* Patients on atypical antipsychotics seem to have insulin secretion phases consistent with  $\beta$ -cell dysfunction. Also, chronicity of antipsychotic treatment predisposes patients with major mental health disorders to central adiposity and low metabolic clearance rate of glucose, a forerunner of glucose intolerance.

**Keywords:** Beta-cell dysfunction ■ Chronic antipsychotic treatment ■ Insulin resistance ■ Major mental health disorders ■ Metabolic clearance rate of glucose

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## INTRODUCTION

Insulin, secreted by the beta-cell of the pancreas, is an anabolic hormone with pleiotropic effects on the liver, skeletal muscle, adipose tissue and brain cells among others.<sup>1</sup> The association between insulin and psychosis was reported decades ago when deep insulin coma therapy was used to treat schizophrenia.<sup>2</sup>

Impairment in insulin action and/or secretion is associated with metabolic disorders such as diabetes, and cardiovascular diseases.<sup>3</sup> It is suggested that physiologic stress, such as mental illness could trigger insulin resistance (IR) peripherally in order to ensure steady supply of insulin and glucose to the brain to prevent neuronal death.<sup>4-6</sup> Shiloah et al.<sup>7</sup> reported that individuals with psychosis have concomitant insulin resistance and  $\beta$ -cell dysfunction, which reverse as the psychosis resolves. Recently, Akinlade et al.<sup>8</sup> also reported a strong association between major mental illnesses and metabolic disorders.

Although the aetiology of IR in major mental illnesses is poorly understood, there is an avalanche of reports suggesting that it is multifactorial.<sup>9</sup> For example, hypothalamic-pituitary-adrenal (HPA) axis activation, hypo-functioning in the central serotonin system, sympathomedullary system, immunological system and the use of depressants are some of the factors associated with insulin resistance in patients with depression.<sup>9-11</sup> Peripheral insulin resistance which usually manifests as hyperinsulinaemia with its associated low glucose utilization, is suggested to be responsible for decreased appetite and weight loss in patients with depression.<sup>9,12</sup> Similarly, glucoregulatory disturbances have been noticed in patients

with schizophrenia even before the advent of antipsychosis.<sup>13,14</sup> However, these disturbances became prominent after the introduction of antipsychotics.<sup>15</sup>

Hyperinsulinaemia and higher insulin resistance are reported to be higher in schizophrenics on antipsychotics compared with schizophrenics not receiving antipsychotic. Interestingly, there was no significant difference in their fasting glucose levels.<sup>14</sup> In contrast to depression and schizophrenia, manic state was associated with increased insulin sensitivity, which was not related to lithium.<sup>16</sup> It however remains unclear if this sensitivity is related to increased physical activity usually associated with mania.<sup>9</sup> In patients with bipolar, fasting and postprandial hyperinsulinaemia as well as elevated HOMA-IR value have been reported. These partly explain the high prevalence of IR and T2DM risk reported in them.<sup>17,18</sup> Furthermore, current use of antipsychotics has been shown to be significantly related to IR which is considered an important factor in resistance to antipsychotic treatment in bipolar disorder.<sup>19</sup>

It is becoming apparent that antipsychotic-induced IR evolves through mechanisms that are somewhat different from the normal mechanisms in diabetes.<sup>20</sup> Johnson et al.<sup>21</sup> showed that antipsychotics cause  $\alpha 2$  antagonism and inactivate muscarinic receptors thereby causing reduction in insulin release induced by acetylcholine (ACh) which subsequently cause hyperglycaemia. Other reports also showed that certain atypical antipsychotics such as olanzapine and clozapine have high affinity for histaminergic, muscarinic, orexigenic and adrenergic receptors which causes increased expression of orexigenic peptides, reduction in lipolytic activity in white adipose tissue, reduction in uncoupling protein-1 (UCP-1) expression and loss of leptin signaling resulting in hyperphagic behavior, fat accumulation, reduced thermogenesis (due to reduction of orexin) and consequently, weight gain which plays an important role in the development of diabetes and cardiovascular diseases.<sup>22–26</sup>

In this environment, there is the dearth of information on IR, beta-cell function, metabolic clearance rate of glucose and their possible interplay with the use and chronicity of antipsychotic treatment in patients with major mental health disorders. This thus, serves as the basis for this study.

## MATERIALS AND METHODS

### Study centre

The study was carried out between January and April 2015 at the New World Psychiatric Hospital, a 60 bedded mental health facility located in South-West Local Government area of Ibadan, Oyo state, Nigeria.

### Study participants and recruitment technique

We recruited consecutive patients who utilized the study centre during the study period that met the inclusion criteria. The first participant was randomly selected, and subsequent ones, consecutively until they were all interviewed. Information on the study participants and their characteristics are already reported.<sup>8</sup> Briefly, 135 adult patients with mental illness were enrolled into the study after which 124 of them with either schizophrenia, depression or bipolar were carefully selected for this study.

### Diagnosis of major mental disorders

The diagnosis of either schizophrenia, depression or bipolar disorder was made using the Structured Clinical Interview for DSM IV Axis I Disorder (SCID) version 2.0<sup>27</sup> to confirm all the initial diagnoses made before the commencement of the study. The diagnosis was allocated by one of us (VOL), a trained psychiatrist.

### Exclusion criteria

We excluded patients who were less than 18 years of age and all those with severe and unstable general medical conditions.

### Ethical approval

The study was approved by the University of Ibadan/ University College Hospital (UI/UCH) Joint Ethics Review Committee while written informed consent/assent was obtained from the participants or their guardians as appropriate.

### Sample collection

Venous blood was collected after an overnight fast (0 min) and at 30 and 120 min post standard 75-g oral glucose tolerance test (OGTT) to determine the plasma levels of glucose and insulin.

### Laboratory analyses

Plasma level of glucose was determined using glucose oxidase method while insulin level was determined using ELISA (Genway Biotechnology, USA) following the manufacturers' instructions.

### Calculation of indices of insulin resistance/ sensitivity

- a. Computer-based homeostatic model assessment (HOMA) index of insulin sensitivity (HOMA2-S%), computer-based homeostatic model assessment (HOMA) index of beta-cell function (HOMA2-B%), and computer-based homeostatic model assessment

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