RISK OF HYPERGLYCAEMIA AND DIABETES MELLITUS IN PERSONS WITH SCHIZOPHRENIA TAKING ANTIPSYCHOTIC MEDICATIONS IN UYO, SOUTH-SOUTH NIGERIA

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ABSTRACT

BACKGROUND: Treatment of schizophrenia with antipsychotic medications may be associated with increased risks for weight gain, insulin resistance, hyperglycemia, and type 2 diabetes mellitus (T2DM) but the associated risk factors for hyperglycaemia and diabetes in these patients are not fully known.

OBJECTIVE: The aim of our study is to determine the prevalence of hyperglycaemia and diabetes in patients with schizophrenia on antipsychotic medications and the risk factors associated with it.

METHODS: Eighty six patients diagnosed with schizophrenia were evaluated for glucose dysregulation using fasting blood glucose test. Age and sex matched healthy volunteer group of 50 subjects was taken for comparison. Results were interpreted according to American Diabetic Association criteria.

RESULT: Study population had a mean of 34.52±8.9 years, 55.8% was male, and had a weight gain of 11.92±6.2 and a mean fasting glucose of 4.63±0.9 mmol/l compared to controls value of 3.83±0.47 ($p<0.001$). Hyperglycaemia was present in 12.7% of the population. The prevalence of diabetes was 3.4%. The risk of hyperglycaemia in the study population was increased for all class of antipsychotic medications (typical or atypical). Hyperglycaemia was more likely with increased duration of antipsychotic medication use and increased weight gain. There was no association of hyperglycaemia with age, sex, and duration of illness.

CONCLUSION: Treatment with antipsychotic medications was associated with a significantly increased risk for hyperglycaemia. There is the need for routine glucose monitoring during treatment with antipsychotic medications.

KEY WORDS: Schizophrenia, Antipsychotic medications, Hyperglycaemia, Diabetes mellitus, Nigeria

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INTRODUCTION

Schizophrenia is a severe mental disorder characterized by significant impairment in family, social and occupational functioning and a chronic progressive nature requiring maintenance treatment.[1] Despite its relatively low prevalence, the early age at onset and its chronic nature means that schizophrenia is an expensive medical condition to health care systems and constitute a growing public health burden globally.[2,3]

Patients with schizophrenia have a life expectancy 20% shorter than that of the general population, [4] approximately 2/3 of the excess mortality is attributed to comorbid medical illness [5] including conditions such as obesity, Type 2 diabetes and cardiovascular disease.[6-8] Schizophrenia increases the diabetogenic potential in part due to poor nutritional habits, smoking and sedentary life style of sufferers.[9] Reports suggest that patients with schizophrenia appear to have higher rates of impaired glucose tolerance, insulin resistance, and type II diabetes mellitus than the general population.[10] Rates for diabetes mellitus in patients with schizophrenia are approximately double those reported for the general population.[11]

The use of antipsychotic medications, in conjunction with other psychosocial interventions constitutes the cornerstone in the management of many psychotic conditions and they are primarily indicated to

treat acute exacerbations of schizophrenia and to prevent relapses.[12] Both typical and atypical antipsychotics have been associated with increased risk of diabetes mellitus in patients with schizophrenia. An association between antipsychotic medications and diabetes mellitus and/or impaired glucose tolerance was reported in the 1950s, soon after chlorpromazine entered clinical practice.[13] Phenothiazine treatment is reported to be associated with glucose regulatory abnormalities.[14] Recent reports suggest that newer antipsychotic medications also contribute more to clinically significant hyperglycemia. Hyperglycemia, exacerbation of existing diabetes, new-onset type 2 diabetes, and diabetic ketoacidosis have been reported with atypical antipsychotics, especially for clozapine, olanzapine, risperidone, quatiepine, aripiprazole and ziprasidone.[15-19]

The exact mechanism of how antipsychotic medications promote the development of hyperglycemia and diabetes mellitus is unknown. It is assumed that the initiating pathophysiology is weight gain, secondary to centrally mediated increases in appetite. It is widely believed that antipsychotic drugs contribute to weight gain and hyperglycemia via effects mediated by binding to serotonin ($5\text{-}HT_2$), noradenaline, dopamine, and/or histamine receptors. Serotonin activity at receptor sites is a potent satiety signal, with the most implicated receptors being $5\text{-}HT_{1A}$ and $5\text{-}HT_{2C}$. Stimulation of $5\text{-}HT_{1A}$ is associated with an increase in food intake whereas stimulation of $5\text{-}HT_{2C}$ is related to a decrease in food intake. Antagonism of the $5\text{-}HT_{2C}$ receptor can, in turn, lead to an increase in food intake, with most second generation antipsychotics (SGAs) possessing $5\text{-}HT_{2C}$ antagonist activity.[20,21]

The long-term consequences of having hyperglycemia and T2DM include microvascular complications (retinopathy, nephropathy, and neuropathies) and macrovascular complications (atherosclerosis-related coronary heart disease, cerebrovascular disease, and peripheral vascular disease).[22]

While the health and economic consequences of type 2 diabetes are widely known, less is known about the contribution of medications to the development of hyperglycaemia and type 2 diabetes mellitus in antipsychotic medicated population of persons with schizophrenia. Studies that evaluate glucose dysregulation in schizophrenia in Nigeria are few; therefore this study was conducted to determine the magnitude of glucose dysregulation in patients with schizophrenia on antipsychotic medications. A healthy volunteer group matched for age and sex variables, and various anthropometric measures was used as control group.

MATERIALS AND METHODS

Location of the study:

This study was conducted at University of Uyo Teaching Hospital from July 2017 to December 2017. The hospital is located in Uyo, the capital city of Akwa Ibom State, Nigeria. All diagnoses made in the institution were according to the tenth edition of the International Classification of Diseases and health-related disorders (ICD -10) criteria.[23] Clinically generated data for each subject enrolled were matched to the ICD -10 criteria.

Subjects. The sample size was calculated using a public domain software available on-line **(**www.statpages.org**)** [24] using a prevalence of hyperglyceamia following antipsychotic treatment as determined from previous Nigerian study (12.4%).[25] The sample consisted of ninety one participants but only eighty six (n=86) subjects with schizophrenia were included in the analysis because 5 subjects had incomplete data. A subject is enrolled if he/she met the following inclusion criteria: a diagnosis of schizophrenia as confirmed by a consultant psychiatrist using the ICD 10 criteria, who has been receiving anti-psychotic medications for at least one year prior to study entry, adults above the age of 18years, and who granted consent. The exclusion criteria were: refusal to give consent, acute or chronic medical conditions including history of diabetes mellitus, malignancy, epilepsy, endocrine conditions,

pregnancy, contraceptives, narcotics, corticosteroid or spironolactone therapy, sedative hypnotic withdrawal, beta-blockers, thiazide diuretics etc

Procedure. Ethical approval for the study was obtained from the Research and Ethical Committee of the University of Uyo teaching Hospital. Informed consent was obtained from patients or their accompanying family members. Patients who met the inclusion criteria were consecutively recruited into the study after a comprehensive psychiatric evaluation and diagnosis by resident doctors in psychiatry. The Mini International Neuropsychiatric Interview (MINI) English Version 5.0.0 [26] was further used to confirm the diagnosis of schizophrenia in the participants. The MINI was designed as a brief structured interview for the major Axis 1diagnosis in the Diagnostic and Statistical Manual (DSM-IV) and ICD-10.

Measures

Socio-demographic characteristics

A socio-demographic questionnaire designed by the authors was used to obtain information Measures evaluated includes socio-demographic details (age of the patient and family member, gender, educational status, marital status, religion) illness related variables (total duration of illness) and medication related variables (type of medication, doses and the chlorpromazine equivalent of the antipsychotic medications)

TABLE 1 SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

Variables	n (%)
Age in years (mean ±SD)	34.52±8.9
Age	
>40 years	45(52.3)
≤40 years	41(47.7)
Sex	
Male	48(55.8)
Female	38(44.2)
Marital status	
Single/separated/widowed	68(79.1)
Married	18(20.9)
Educational level	
Primary	6(7.0)
Secondary	56(65.1)
Tertiary	24(27.9)
Employment status	
Employed	21(24.4)
Unemployed	65(75.6)
Duration of illness	
≤8 years	62(72.1)
>8 years	24(27.9)
Mean duration of Antipsychotic use (years)	5.71 ±2.4
Class of antipsychotic medication	
Conventional	22(25.6)
Atypical	28(32.5)
Combination	36(41.9)
Body Mass Index (BMI)	
Underweight	2(2.3)
Normal	21(24.4)
Overweight	47(54.7)
Obese	16(18.6)

The mean duration of illness was 6.95±6.17 years and the mean duration of use of antipsychotic drugs 5.71±2.4 years. Mean weight gain of study participants was 11.92±6.2kg (difference in weight between first hospital visit for treatment and entry into study) after mean 5.71±2.4 years of antipsychotic medication use.

Medication profile

The medication profile of each individual patient was obtained through chart review of the medication record files domiciled in the hospital. Data recorded include: The number of antipsychotic medicines on the patients' current treatment regimen. Exposure to antipsychotic medication was measured as 1.class of antipsychotics used 2, duration of antipsychotic use 3, doses of medication used. All the antipsychotics used by the test subjects were converted to their chlorpromazine equivalent doses.

Analysis of blood samples.

In this study, fasting plasma glucose was measured by the same technician designated for this purpose. When a subject had pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ⩾ 126 mg/dl), he/she was assumed to have impaired fasting glucose.

Data Analysis:

Descriptive statistics such as frequencies, mean and standard deviation were computed for socio-demographic and clinical characteristics of the participants and other variables as appropriate. Relevant inferential statistics such as chi-square, t-test, ANOVA and Pearson's correlation were used to determine the relationship between outcome and independent variables. The statistical package for social sciences (SPSS) version 20 was used for analysis. Significance was computed at $p < 0.05$.

RESULT

One hundred participants, comprising 86 cases and 50 controls were included in the study. The mean age of the cases was 34.52 ± 8.9 years (range 20-60 years). The mean age of the controls was 33.84±8.2 comprising 23 males and 27 females. Regarding the cases, more than half of them were females (57%). The majority (79.1%) was never married and about 72.1% of them had formal education to at least secondary school level and 75.6% of them were unemployed.

DISTRIBUTION OF THE ANTIPSYCHOTIC-RELATED VARIABLES

About 24.4% of subjects were on conventional antipsychotics and the three most commonly prescribed first generation antipsychotics were: haloperidol (45.3%) stelazine (22.8%) chlorpromazine (20.6%). The remaining 11.3% were on thioridazine and long acting injectables like Fluphenazine decanoate or Flupenthixol decanoate.

About fifteen percent (15.1%) of the subjects were on atypical antipsychotics. The most commonly prescribed serotonin dopamine antagonists (SDAs) were olanzapine (43.4%), risperidone (50.2%), quatiepine (3.1%) aripiprazole (2.5%) clozapine (0.8%). Over 52.0% of the subjects were on polytherapy and the most common combinations were: any class of antipsychotics like combination of two conventional antipsychotics or conventional antipsychotics and atypical and any class of antipsychotics and long acting injectables. The dosing frequency of 52% of the subjects was at least twice per day and 25% were on once daily dose regimen.

The mean daily dosage per day in milligram for subjects on chlorpromazine was 320 mg/day. The subjects on haloperidol had 15.40 mg/day mean value while those prescribed stelazine 12.80 mg/day. The mean chlorpromazine equivalent dosage was 512.82mg and 256.0mg for those on haloperidol and stelazine respectively.

The mean daily dosage for olanzepine was 17.35±2.8. mg/day. Subjects on risperidone received a mean daily dosage of 3.65±1.5 mg/day The chlorpromazine equivalent dosage for patients on olanzapine and risperidone was 347.0mg and 365mg respectively.

ANTIPSYCHOTIC USAGE AND WEIGHT GAIN

The mean weight gain of the subjects on antipsychotic medications (determined as the difference between weight at first presentation before commencement of antipsychotic medications and weight at

study entry) was 11.92±6.17kg over a mean 5 year period. By BMI values, 2.3% were underweight, 24.4% of subjects had normal weight, 54.7% were overweight and 18.6% subjects were obese. There was correlation between period of antipsychotic use and weight gain (r=0.23, p=0.03). Based on class of medication, there was no statistically significant difference in the mean weight gain (between subjects on atypical antipsychotics and conventional antipsychotics though the greater mean weight gain was related to the atypical class of antipsychotics (p=0.11).

TABLE 2. GLYCAEMIC STATUS OF CASES AND CONTROL SUBJECTS

Fasting blood sugar status	Cases (Test subjects)	Control subjects	statistics
	Proportion(%), mean(SD)	proportion(%), mean(SD)	
Normal	72(83.7) 85.97±19.4	69(93.2) 70.85±1.27	t=5.9 **p<0.001**
Prediabetes	11(12.7) 110.20±10.4	3(4.1) 102.0±0.69	t=2.6 **p=0.03**
Diabetes	3(3.4) 145.76±8.42	2(2.7) 141.26±1.4	t=1.15 p=0.31

Blood Glucose profile and associated factors

The mean fasting glucose of the cases was 4.63±0.91 mmol/l and the controls was 3.83±0.47 mmol/l. the difference between both group was statistically significant (t=7.31, p<0.001).

TABLE 3. INDEPENDENT RISK FACTORS FOR HYPERGLYCAEMIA

Variables	Hyperglycaemia			
	No N(%)	Yes N(%)	Statistics	P-value
Gender				
Male	40(83.3)	8(16.7)	x^2= 0.02	0.91
Female	32(84.2)	5(15.8)		
Age				
>40	34(82.9)	7(17.1)	x^2=0.036	0.85
≤40	38(84.4)	7(15.6)		
Duration of illness				
≤8yrs	53(85.5)	9(14.5)	x^2= 0.50	0.47
>8yrs	19(79.2)	5(20.8)		
Class of antipsychotic medications (Mean, SD)				
Conventional	72.53±12.63	117.00±20.63	t=-6.2	**<0.001**
Atypical	85.87±7.39	116.73±24.5	t=-4.6	**<0.001**
Combination	76.53±12.63	117.53±20.75	t=-7.9	**<0.001**
Class of antipsychotics				
Conventional	20(90.9)	2(9.1)	x^2=2.17	0.34
Atypical	24(88.9)	4(11.1)		
Combination	29(78.4)	8(21.6)		
Duration of antipsychotic use				
≤5 years	45(91.8)	4(8.2)	x^2= 5.50	**0.02**
>5 years	27(73.0)	10(27.0)		
BMI				
Normal/low	20(87.0)	3(13.0)	x^2= 6.56	**0.04**
Overweight	42(89.4)	5(10.6)		
Obese	10(62.5)	6(37.5)		

In the study population (cases), we found 83.7% with normoglycemia, 12.7% with hyperglycemia (prediabetes) and 3.4% with diabetes. Among the controls, 93.2% had normal fasting glucose values. 4.1% of controls had values in the prediabetic range and 2.7% were in the diabetic range. The differences between the cases and control in the prediabetes range was statistically significant (p=0.03). The risk of hyperglycaemia was significantly related to the duration of antipsychotic use (p=0.02) and the degree of weight gain (p=0.04).

The subjects in the older age group were as likely to develop antipsychotic induced hyperglycaemia as subjects in the younger group (p=0.85). Also, there was no significant differences in the means of subjects on conventional antipsychotics only, atypical only and those on combination (both conventional and atypical) antipsychotics (ANOVA (F)=0.50, p=0.60). The subjects on atypical antipsychotics were as likely to have hyperglycaemia compared to the subjects on conventional antipsychotics (t=1.17, p=0.60). No significant differences were found by sex (p=0.91), and BMI scores (p=0.50)

Among the cases that received atypical/conventional combination antipsychotics 8 cases representing 21.6% developed hyperglycaemia and among those that received atypical antipsychotics, 3 cases representing 11.1% developed hyperglycaemia and among those that received conventional antipsychotics only, 2 cases representing 9.1% developed hyperglyceamia (x^2=2.12, p=0.34). The mean fasting glucose value of four individual antipsychotic medications was stelazine 79.20±15.01, haloperidol 79.83±20.64, risperidone 89.41±19.71 and olanzepine 91.06±15.64. There was no significant difference among the individual medications on their effect on the fasting glucose status (ANOVA (F)=1.93,P=0.38)

DISCUSSION

Treatments with antipsychotic medications in our study were associated with significant impact on fasting glucose status of study participants when compared with the healthy controls. There was significantly increased risk of developing hyperglycaemia among subjects following treatment with both conventional and atypical antipsychotics medications. Previous studies worldwide have consistently reported increased risk of hyperglycaemia in antipsychotic medicated populations compared to the general patient population.[27,28] According to the American Diabetes Association (ADA) any individuals with fasting glucose level of 100-125mg/dl (5.6-6.9 mmol/l) or glucose level of 140-199mg/dl (7.8-11 mmol/l) two hours after 75-g oral glucose tolerance test or hemoglobin A(1c) 5.7%-6.4% be classified as prediabetic, indicating increased risk for the emergence of diabetes [29]

The prevalence of hyperglycaemia in this study was 12.7% after six years mean duration of antipsychotic medication use. The prevalence rate of hyperglycaemia of our sample is comparable to that reported in two previous Nigerian studies [25,30] and in disagreement with other studies which had reported much higher prevalences.[31-35.] Differences in study design may in part, account for these differences in reported rates.

While the causal links between the degree of weight gain and hyperglycaemia is not direct, plausible reasons why the glucose dysregulation in our sample was significantly higher than the healthy controls may not be totally unrelated to the degree of antipsychotic medication induced weight gain observed in this study. A high proportion of the participants, about half of the subjects in this study had remarkable increases in weight gain which was related to the duration of antipsychotic medication use. Also, life-style issues that may include redundancy and sedentary living noted among participants may be contributory.

There is considerable variability worldwide in the reported prevalence of hyperglycaemia and diabetes mellitus associated with the individual antipsychotics medications. These differences in prevalence rates may partly reflect differences in study design, definition and estimation of plasma glucose and characteristics of the study population.

In our study, we found a significantly increased risk of hyperglycaemia for both typical and atypical antipsychotic medications compared to matched controls. Several studies have reported similar finding. [7,10] Our findings however, differed with that of Hagg et al [36] who found no significant difference in the prevalence of hyperglycaemia and diabetes, based on class of medication, between patients on typical antipsychotic medication and atypical (clozapine). Newcomer et al [37] found a significant increase of glucose level for atypical (olanzepine and clozapine) in comparison with typical antipsychotics and healthy controls.

In this study, the degree of glucose dysregulation was related to the duration of antipsychotic use and the degree of weight gain. This is consistent with previous studies

which had reported similar findings. [34,38-40] The medications most associated with hyperglycaemia are also those that induced the greatest amount of weight gain. The mean hyperglycaemia values were higher for the atypical medications compared to the conventional drugs. Also, the mean weight gain induced by the atypical medications was higher than that attributed to conventional medications. Obesity is an established risk factor for developing hyperglycaemia and type 2 diabetes mellitus. [19,41,42] About 73.3% of our sample had BMI score in the overweight and obese range. Also, the fact that a high proportion of participants in our sample are unemployed, may translates to a greater degree of sedentary life-style and under activity which is a known risk factor for weight gain and diabetes mellitus. [43]

The clinical implication of these gluco-regulatory abnormalities in patients on these medications especially in a third world healthcare setting is the additional cost burden of care.[44] It becomes imperative in the management of patients with schizophrenia, some of whom may be on medication for a long duration, to monitor this metabolic adverse event and switch to antipsychotic agents with lower risk potential for hyperglycemia, dyslipidemia, and/or substantial weight gain in the course of treatment.[27] The public health implications are tremendous due to the large number of adult patients treated with these agents. There is a compelling need for regular and routine monitoring of all patients on these medications.

This study has some limitations. First being a cross-sectional study and cannot confirm associations between the factors studied, the value must be limited to the descriptive and its exploratory nature. Also, only the fasting plasma glucose (FPG) test was used to evaluate undiagnosed hyperglycaemia in this study. The oral glucose tolerance test (OGTT) would have yielded increased sensitivity and specificity of the impaired glucose assessment.[34]

CONCLUSION:

Patients on antipsychotic medication for schizophrenia or other illnesses should be considered a high-risk group for hyperglycaemia and diabetes. Current use of conventional or atypical antipsychotics is associated with a generally increased risk of type 2 diabetes which seems to vary with medication.

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