OPTIMIZATION OF EARLY DIAGNOSIS OF GLUCOSE METABOLISM IMPAIRMENT FOR PATIENTS RECEIVING ANTIPSYCHOTIC MEDICATIONS AT OUTPATIENT PSYCHIATRIC CLINIC OF THE UNIVERSITY TEACHING HOSPITAL

BY

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DECLARATION

I, Pandu Makame Haji, do hereby declare that this dissertation is my original work and that it has not been presented and will not be presented to any other learning institution for a similar or any other degree award.

Signature…… Date……

CERTIFICATE OF APPROVAL

This dissertation of Pandu Makame Haji has been approved as partial fulfillment of the requirement for the award of the Degree of Master of Medicine in Psychiatry by the University of Zambia.

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ABSTRACT

Patients using antipsychotic drugs are more likely than the general population to suffer glucose metabolism dysfunctions, yet these problems are frequently overlooked. According to several research findings, patients who take antipsychotic drugs, particularly second-generation antipsychotics, are four times more likely to develop overweight, obesity, and diabetes type 2. Furthermore, studies have indicated that failing to recognize these metabolic issues puts an individual at risk of getting comorbid disorders such as cardio-metabolic diseases and others which potentially worsen psychiatric problems. For controlling and enhancing potential psychiatric treatment outcomes, early diagnosis and treatment of glucose metabolism dysfunction is crucial. Between June and September 2021, a descriptive cross-sectional study was conducted at the University Teaching Hospital outpatient psychiatric clinic to optimize the early diagnosis of glucose metabolism deficits in patients with psychiatric disorders taking antipsychotic medications. A systematic sampling method was applied to all patients who were receiving antipsychotic drugs. All participants were checked for their weight, height, Body Mass Index (BMI), waist circumference, random and fasting blood glucose levels, respectively. The results were analyzed by using SPSS software versions 20, while Fisher's exact test was used to determine the relationship between categorical variables. A total of ninety patients with psychotic disorders aged 18 years and above were recruited for the study; 47.8% were male and 52.2% were female. 26.7% were overweight (BMI 24.5-29.5kg/m2), 14.4% were obese (BMI>30kg/m2) and 11.1% were under weight (BMI <18.5kg/m2), and 38.9% had higher waist circumferences. The proportion of individuals with impaired fasting blood glucose levels found in this study was 11.1% and that of individuals with diabetes was 10.0%, respectively which is higher compared to the general population. Patients who were receiving second-generation antipsychotics showed a slightly higher proportion of impaired fasting blood glucose levels compared to those on conventional antipsychotic medications. Increased waist circumference and increased age were significant factors associated with impaired glucose metabolism. It is, therefore, recommended that screening of glucose metabolic parameters should be a routine practice by psychiatrists and other health professionals working in psychiatric clinics before treatment with antipsychotic medications is started; there should be a regular follow up and monitoring of glucose

metabolic parameters for all patients who are on treatment with antipsychotic medications. Education on a healthy lifestyle should also be disseminated in every visit, multidisciplinary approach involving other specialists input like physician and endocrinologist should always be applied to all patients who are diagnosed with glucose metabolism impairments.

Key words: *Antipsychotic medications, Psychotic disorder, impaired glucose metabolism, Body Mass Index, Waist circumferences*

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DEFINITIONS

Antipsychotics means synthetic molecules used to treat psychosis

Body mass index (BMI) is a person's weight in kilograms divided by the square of height in meter

Impaired fasting blood glucose (IFBS) if the body does not able to regulate glucose efficiently

ABBREVIATIONS

APD	Antipsychotic drugs
BMI	Body Mass Index
DSM 5	Diagnostic Statistical Manual 5
DSM IV	Diagnostic Statistical Manual 4
FBS	Fasting Blood Sugar
FGA	First Generation Antipsychotic
ICD 10	International Classification of Disease 10
IDF	International Diabetic Federation
NHRA	National Health Research Authority
RBG	Random Blood Glucose
UNZABREC	The University of Zambia Biomedical Research Committee
UTH	University Teaching Hospital
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist Hip Ratio

CHAPTER ONE

1.0 Overview

This chapter describes the background of the study, statement of the problem, rationale, and objectives of the study.

1.1 Background of the Study

Antipsychotic drugs revolutionized the lives of many patients with psychotic disorders and other form of mental illnesses since introduced in the 1950s, but they were hampered by the emergence of crippling and stigmatizing extrapyramidal side effects and movement disorders (Xu and Zhuang, 2019).

Because of their enhanced efficacy and side effect profile, atypical antipsychotic medications have recently been promoted as first-line treatments for serious mental illness (Sliwa *et al.*, 2014).

However, due to widespread concerns about the link between atypical antipsychotics and metabolic side effects (Jeon and Kim, 2017), psychiatrists are questioning whether the shift to atypical antipsychotic medications have simply resulted in the substitution of one set of problems for another, potentially leading to generalized deterioration of patients' physical health and poor psychiatric outcome (Santini *et al.*, 2016).

These metabolic side effects are sometimes linked to genetics and other modifiable factors such as sedentary lifestyles, physical inactivity, and patients' lack of dietary knowledge (Wei *et al.*, 2016).

Furthermore, patients receiving treatment with the most efficacious antipsychotic drugs such as clozapine and olanzapine are associated with an increased risk of weight gain, obesity, and other forms of glucose metabolism impairment like reduced insulin sensitivity (Dasgupta *et al.*, 2017) which all signify the glucose metabolism derangement and can lead to other life-threatening cardiovascular morbidity (Panagiotopoulos, Ronsley, and Davidson, 2009). People with psychiatric disorders have an increased risk of developing persistent hyperglycemia, leading to diabetes

type 2 which is the main contributing factor to cardio-metabolic abnormalities (Olsson *et al., 2015*).

While it is known that there are multiple causality and risk factors for these problems, some of the newer antipsychotic drugs like olanzapine have been singled out as the major cause of glucose metabolic irregularities (Hammoudeh *et al*., 2018)

Several modalities and approaches have been applied to study these medications specific risk for detrimental effects on glucose metabolism impairments during treatments (Burghardt *et al.*,2016), while abnormal increasing of waist circumferences and body mass index have been identified as a good predictor of these metabolic side effects (Kaushal, Bhutani, and Gupta, 2012).

Olanzapine is one of the notorious atypical antipsychotic drug which is associated with the most severe form of glucose metabolism consequences like weight gain (Martins, Haas, and Obici, 2010), obesity, and higher fasting blood glucose levels (Cottingham *et al.,* 2006). However, glucose dysregulation and reduced insulin sensitivity in patients with psychotic disorders who are using antipsychotic medications can occur independent of weight gain (Deng, 2013).

It is now well established that, people with serious mental illness, have excess morbidity and mortality leading to a reduced lifespan by about twenty years compared with the general population (Li *et al.,* 2018). The increased mortality is largely attributable to physical illness, including glucose metabolism abnormalities and cardiovascular disease, rather than factors that are directly associated with psychiatric illness such as suicide or homicide (Owusu-Ansah *et al*., 2018). Generally, metabolic abnormalities occur in about 20 to 60% of patients with chronic psychiatric disorders which increases the three-fold risk of developing diabetes type 2 in those patients treated with antipsychotic medications (Riordan, Antonini, and Murphy, 2011).

The abnormalities not only confer an elevated risk of cardio-metabolic illnesses and increased mortality but are also associated with poor psychiatric and functional outcomes for the patients (Mhatre V. Ho and Kelsey C. Martin, 2012).

These metabolic abnormalities vary between different agents, with patients receiving atypical antipsychotic drugs which are known as second-generation antipsychotic

medications like olanzapine and clozapine being much more likely as compared to those on first-generation antipsychotic drugs (Chen *et al.*, 2017).

It was found that about 30% of cases of glucose metabolism impairments resulting from reduced insulin sensitivity developed as a result of antipsychotic drugs tend to be undiagnosed (Houseknecht *et al.*, 2007), and approximately 10% of patients treated with antipsychotics are at risk of developing glucose metabolism impairment and diabetes type 2 (Volpato and Zugno, 2013). While there was limited information of glucose metabolism impairment in patients with psychotic disorders in Zambia, this study was intended to optimize the early diagnosis of glucose metabolism impairments for patients with psychiatric disorders receiving antipsychotic medications at the psychiatric clinic of the University Teaching Hospital in Lusaka.

1.2 Statement of the problem.

Over the last three decades, the prevalence of metabolic diseases has dramatically risen worldwide. About 4.8% of people are estimated to be living with impaired glucose metabolism, and the risk of glucose metabolism effects are higher in patients with mental disorders than in the general population (Whicher, Price, and Holt, 2018). In sub-Saharan Africa, approximately 75% of people living with glucose metabolism irregularities, including diabetes type 2, remained undiagnosed, resulting in a large number of untreated cases, poor glycemic control, and the consequences of poor psychiatric treatment outcomes (Daniel *et al.***,** 2017).

In 2011, the prevalence of glucose metabolism impairment was 4.0% among the Lusaka adult population aged 25-34 years (Nsakashalo-Senkwe *et al.*, 2011), and diabetes mellitus was 3.5% in the Zambian general population (Bailey *et al.*, 2016), though no data have been published for patients with psychiatric disorders in particular, and the proportion is likely to be unknown.

However, antipsychotic drugs have been used as a mainstay of treatment in psychiatric practice for a wide range of psychotic disorders, and they are the leading cause of glucose metabolic irregularities in these patients (Zhang *et al.*, 2017). It is clearly known that, there is an increased awareness among mental health providers of the increased chance of glucose metabolism syndrome in psychiatric patients due to

antipsychotic medications, though rates of screening, diagnosis, and treatment remain poor (Annamalai and Tek, 2015).

The diagnosis of glucose metabolism disorders in these patients, on the other hand, is extremely rare. This could be due to ineffective clinical practices that do not prioritize early screening and diagnosis of the problems, or it could be related to the complexity of psychiatric illnesses themselves. Failure to recognize these risk factors linked with aberrant glucose metabolisms, such as impaired fasting blood glucose and reduced insulin sensitivity, leads to the early onset of diabetes type 2 and its consequences, such as heart disease and others (Daniel *et al.*, 2017).

Therefore, this study was intended to optimize the early diagnosis of glucose metabolism impairment in Zambian patients with psychotic disorders who were receiving antipsychotic medications at the outpatient psychiatric clinic of the University Teaching Hospital in Lusaka, Zambia.

1.3. Rationale of the study

Patients with psychotic disorders who are taking antipsychotic drugs have a significant rate of developing glucose metabolism impairment. It's also possible that the prevalence of this problem is very high in this population group. However, the impact of this problem is underestimated since psychiatrists and medical professionals working in mental health services are not regularly involved in routine screening and diagnosis of these problems at the appropriate time. While various reviews have suggested and concluded that patients receiving antipsychotic drug treatment require active routine physical health screening (Yogaratnam *et al.*, 2013), this practice has not been prioritized in our daily practice.

Therefore, the results of this study can later be used to measure the burden of the problems of glucose metabolism impairment in patients with psychiatric disorders in Zambia, which will facilitate improvement in the practicing habits of medical professionals in psychiatric practices and improve the outcomes of patients as well.

1.4 . Study questions

1.4.1. What is the proportion the demographic characteristics of patients with glucose metabolism impairments in patients treated with antipsychotic medications?

1.4.2. Is there any relationship between the duration of antipsychotic treatment and the development of glucose metabolism impairments?

1.5. General objective of the study.

To optimize the early diagnosis of glucose metabolism impairments in patients with psychiatric disorder treated with antipsychotic medications.

1.5.1 Specific objectives.

1.5.1.1 To determine the demographic characteristics and proportion of patients with psychotic disorder who developed early glucose metabolism impairment when treated with antipsychotic medications.

1.5.1.2 To determine the association between glucose metabolism impairment and type of antipsychotic medication used.

1.5.1.3 To determine the relationship between duration of antipsychotic use and development of glucose metabolism impairments in patients receiving antipsychotic medications.

CHAPTER TWO

2.0 Overview

This chapter contains a review of the literature on the problem of glucose metabolism impairment in different parts of the world including some parts of Sub-Sahara African countries.

2.1 Literature review

2.1.1 General aspect of Antipsychotics use and glucose metabolic change.

Long-term administration of antipsychotic drugs is known to cause glucose metabolism dysregulation, which was demonstrated during epidemiological investigations in both human and animal studies (Boyda *et al.***,** 2013, Kowalchuk *et al.,* 2019). A recent study of 307 patients with psychotic disorders conducted in America showed that atypical (second-generation) antipsychotic drug like olanzapine caused glucose metabolic disorder, which was manifested by type 2 diabetes (17%), obesity (48%), dyslipidemia (35%), and hypertension (32%), with a mean treatment duration of 7.6 years, while other antipsychotics also induced similar metabolic side-effects (Reed *et al.,* 2014). Another study has shown that antipsychotic drugs caused 37% of prediabetes cases and 10% of diabetes mellitus type 2 (Manu *et al.,* 2012). Furthermore, the European First-Episode Schizophrenia Trial (EUFEST) reported a 20–30% incidence rate of glucose metabolism abnormalities such as hyperglycemia after one year of treatment with olanzapine, quetiapine, and ziprasidone, with no significant differences between these antipsychotic medications (Fleischhacker *et al.,* 2013).

A comparison of 28,858 patients with mental disorders treated with antipsychotic drugs and 14,429 healthy controls, not on antipsychotic drugs showed that the risk of glucose metabolic syndrome and diabetes increased threefold in individuals treated with antipsychotic drugs compared to the healthy control group (Bobo *et al.***,** 2013). Thus, antipsychotics' effects of metabolic disturbances and diabetes type 2 have been confirmed in animal models as well (Luo *et al.,* 2019), while in another study, olanzapine and clozapine have been shown to decrease the plasma level of insulin

and cause impaired glucose metabolism manifested by hyperglycemia and reduced insulin sensitivity in rats (Melkersson, Berinder, and Hulting, 2011).

The major complication of glucose metabolism disorders is diabetes mellitus leading to the development of complicated heart disease (Vancampfort *et al*.**,** 2016). Antipsychotic drugs significantly increase the risk of acute myocardial infarction with an adjusted odds ratio of the risk of 2.52 (95% CI = 2.37–2.68) (Lin *et al.,* 2014). Aykut and colleagues examined the relationship between metabolic disturbances and cardiovascular disease incidence in patients with psychotic disorders on both deport and oral antipsychotic medications including paliperidone, olanzapine, risperidone, quetiapine, clozapine, and amisulpride. They found that these drugs had higher chances of causing both metabolic disturbances including weight gain and glucose intolerance, although oral second-generation antipsychotics had a higher incidence of glucose metabolic irregularities and cardiovascular accidents as compared to deport medications (Aykut and Karagüzel, 2018).

Recent attention has also been focused on antipsychotic-induced hyperglycemic emergencies. Patients treated with atypical antipsychotic medications have a higher risk of developing diabetic ketoacidosis than individuals on conventional antipsychotic medications (Ingimarsson *et al.,* 2017). Lipscombe and colleagues conducted a multi-center retrospective cohort study that enrolled 725,489 patients on antipsychotic medications to investigate hyperglycemic emergencies (hyperglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state) experienced by new users of risperidone, olanzapine, and other typical and atypical antipsychotic drugs. The results showed that hyperglycemic emergencies were 1 per 1,000 people in patients aged 18–65 and 2 per 1,000 people in those older than 65 years of age. The events were much more frequent in patients with pre-existing diabetes, 6–12 per 1,000 people. It was similar in the risk of hyperglycemic emergencies with the initiation of olanzapine versus risperidone (Lipscombe *et al.*, 2014).

In brief, both clinical and animal studies have shown that antipsychotic drugs can cause serious glucose metabolism side effects, including hyperglycemic emergencies, and other forms of glucose metabolic abnormalities like glucose intolerance, hyperglycemia, and type 2 diabetes mellitus which is a major risk of cardio-metabolic disease leading to the occurrence of unexpected premature death

(Li *et al.***,** 2018). However, it is worth noting that the risk of type 2 diabetes in the adolescent population and youth treated with antipsychotic drugs has been underestimated (Samaras *et al.,* 2014). Understanding the underlying mechanisms and associated risk factors will be important for preventing and treating these side effects and thus improving the clinical outcomes of patients taking antipsychotic drugs (Kowalchuk *et al.,* 2019).

2.1.2 Gender differences in glucose metabolism impairments and antipsychotic use.

A large body of clinical research has associated female sex with an increased risk of metabolic side effects, including weight gain, compared to males (Castellani *et al.***,** 2019). Some examples of those are studies that enrolled a larger number of patients on either clozapine or olanzapine, the two notorious APs known to be associated with the highest rates of weight gain (Castellani *et al.,* 2019). This was also seen in a study done by Lau *et al.,* (2017), which compared weight gain among 110 patients (average age of 34.5) with schizophrenia taking atypical antipsychotic medications. It was identified that the female sex is a risk factor for significant weight gain after 3 to 12 months of therapy. Females gained +5.5% of their body weight, while males gained +1.3% (P = 0.01).These results are in agreement with a study from 2004 that compared weight gain among patients randomized to open-label clozapine **vs.** continuation with first-generation antipsychotics. Patients treated with Olanzapine and clozapine gained more weight (Dayabandara *et al.,* 2017), than patients maintained on conventional antipsychotics (FGA) over 2 years, and the weight gain was significantly higher in women than in men. Data retrospectively analyzed from 3,826 patients involved in olanzapine clinical trials also identified female sex among other risk factors (e.g., younger age and lower baseline body mass index (BMI) for increased weight gain associated with olanzapine use (Lau *et al.,* 2017).

In another recent study, which recruited 119 patients between the ages of 8 and 19 years with schizophrenia or schizoaffective disorder, revealed different results, whereby sex was not found to be a predictor or moderator of weight change over eight weeks of receiving second-generation antipsychotic medications (SGA). Susilova *et al.,* (2017) observed that men were more likely to gain weight than women when they compared 462 patients (average age of 30 in males and 38.3 in

females) with schizophrenia or schizoaffective disorder in the Czech Republic. Similar results were identified in a study of 123 Han Chinese patients with schizophrenia (average age of 34) treated for up to 42 days with risperidone.

Though there was a significant heterogeneity in trials with respect to several factors, including study population, duration of current treatment, specific agent used, and past medication exposure, that may explain the conflicting results (Susilova *et al.*, 2017).

2.1.3. Diabetic mellitus and glucose metabolism impairment in patients with psychotic disorders.

Diabetes mellitus is a kind of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Zhang *et al.*, 2017), with exponential increases in both developed and developing countries (Gebreegziabiher, Belachew, and Tamiru, 2020). In 2016, around 422 million adult people were living with diabetes in the world (Mwila, Bwembya, and Jacobs, 2019). This number is expected to be two times higher by the year 2030 (Nyoni *et al.*, 2018). It was also reported that the global prevalence of diabetes mellitus was approximately 8.5%, with Middle East countries like Kuwait, some other Arabian countries, and northern parts of Africa being in the top ten of all diabetic cases in the world (Karim *et al.*, 2021).

Research results found that there was a higher rate of new cases in patients with severe mental disorders like schizophrenia who were diagnosed with diabetes type 2 (Hsu *et al.*, 2011), with a prevalence of about 6.2% to 8.7%, which is higher compared to the general population (Nuevo *et al.*, 2011, Nanasawa *et al.*, 2017). It has become a great concern of public importance for patients with mental disorders, particularly in low-resource countries like Africa, which has around 85% of all undiagnosed cases of diabetes mellitus (Nyoni *et al.*, 2018). Though little is known about the consequences of these problems of delaying the diagnosis and detection of cases, proper monitoring and timely management of this problem and other physical illnesses improves the outcome of patients with psychotic disorders (Olsson *et al.*, 2015).

2.1.4 Diagnosis of diabetes mellitus, indications and biomarkers.

Degenhardt, Lynskey, Hall, and Wayne (2002) reported that the traditional biochemical measurements for initially detecting patients with diabetes mellitus are random estimations of blood and urine glucose concentrations. According to American Diabetic Association (ADA) FBS >7.0 mmol/dl is the diagnostic value of diabetes (Inzucchi *et al.*, 2012).

Furthermore, since these indicators fluctuate continuously since factors such as dietary intake and environmental stress may affect someone's glucose metabolism processing, it is very difficult to evaluate glycemic control correctly by taking measurements at a single visit (Suzuki *et al.*, 2014). Accurate detection requires careful standardization of both the time of day that the sample is collected and the time after carbohydrate ingestion as part of the practice of assessing oral glucose tolerance tests. Previously, glycemic control was evaluated by plasma glucose or urinary glucose (Tamura *et al.*, 2013).

To prevent chronic diabetic complications, it is necessary to try to optimize the diagnosis of glucose metabolism impairment as much as possible. Thus, monitoring glucose fluctuation is important to avoid poor glycemic control and its consequences on patients' physical health (Krhač and Lovrenčić, 2019), even in those who do not have psychiatric conditions and are not on antipsychotic medications. Monitoring by biomarkers has a key role in the assessment of glycemic control in psychiatric patients as well (Krhač and Lovrenčić, 2019).

2.1.5 Antipsychotic medications and Glucose metabolism impairments.

A study conducted by Sugai *et al.,* **(**2012) titled "Excessive Insulin Secretion in Japanese Patients with Schizophrenia Treated with Antipsychotics Despite Normal Fasting Glucose Level" was a cross-sectional study with the main objective of examining the effect of antipsychotic medications on the glucose-insulin response before and after glucose loading. The study enrolled 204 hospitals that admitted patients with psychotic disorders who met the DSM IV criteria for the diagnosis of schizophrenia. The patients admitted from medical and dental hospitals affiliated with Niigata University and from the other five hospitals dealing with the treatment of psychiatric patients in Niigata prefecture, and about 148 health staff as a control

group, were nondiabetics with no history of other glucose metabolic illnesses. All participants were matched for age, sex, and body mass index at the time of recruitment. Also, the participants were required to have been treated with some antipsychotics for at least eight weeks with no other drugs except benzodiazepine as an adjuvant treatment and no drug dosage adjustment for about three weeks before the beginning of the study.

An oral glucose tolerance test was done in 148 patients treated with second-generation antipsychotics and 11 patients on conventional antipsychotics, together with 90 healthy control individuals. The plasma insulin and serum glucose levels were checked and recorded at 0 min, 30, 60, 90, and 120 minutes. Similarly, body mass index and waist circumference were calculated and the results were compared between the two groups.

The result of this study showed no significant findings in age and body mass index between the two groups. However, there was a marked increase in waist circumference in patients with schizophrenia treated with antipsychotic medications (P = 0.001) as compared to healthy individuals. Furthermore, plasma glucose and serum insulin levels in antipsychotic-treated patients were significantly higher (P = 0.001 and P = 006, respectively) after 30, 60, 90, and 120 minutes of the test when compared to the control group.

With these results, it was confirmed that patients with schizophrenia treated with antipsychotics exhibited excessive insulin secretion compared with healthy subjects after a glucose load, regardless of the fasting glucose levels and fasting insulin concentrations

Therefore, the study findings strongly concluded and demonstrated the occurrence of glucose metabolism impairment in patients with schizophrenia following antipsychotic treatment, which was manifested by reduced insulin sensitivity as a result of antipsychotic medications. However, the findings of this study have some weaknesses in terms of the study design, being cross-sectional. The author did not compare the adverse effects of individual particular drugs before the beginning of the study because some of these patients had already been using other antipsychotics before the antipsychotics were being studied.

In addition to that, the study did not screen for and explain the possibility of other health conditions like thyroid disease, which has a direct influence on glucose metabolism, the dosage of the drugs, and serum drug concentrations of a particular drug, which also may have significant effects on glucose metabolism in some patients.

Finally, the study only included patients who were admitted to the hospital with limited exercise and dietary control and excluded those with diabetes mellitus at the beginning of the study, regardless of whether their glucose level had been normalized with diabetic medications. This resulted in the study having a small sample size with limited information.

Another study by Wu *et al.*, (2014), was an open-label cross-sectional study with the title "The Comparison of Glucose and Lipid Metabolism Parameters in Drug-Nave, Antipsychotic-treated, and Antipsychotic Discontinuation Patients with Schizophrenia" This study was conducted by the Psychiatry Department of the Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou, Guangdong, People's Republic of China.

From October 2009 to March 2012, 131 admitted patients with schizophrenia participated in the study, which was divided into three groups: 70 first-episode drug nave patients, 33 patients with schizophrenia who had been continuously treated with antipsychotics for one year or more before the start of the study, and 28 patients who had been treated with antipsychotics for one year or more and discontinued for more than 3 months before the start of the study. The study went on to screen and exclude all patients with a history of any other mental illness who did not meet the DSM IV criteria for a diagnosis of schizophrenia, as well as any history of physical illnesses or use of any type of medicine that could have a positive effect on glucose metabolism. Glucose metabolic parameters, including fasting serum glucose level, blood insulin level, and other anthropometric measurements such as weight, height, waist circumference, and hip circumference, were taken before and after the beginning of the study.

From this study, it was found that antipsychotic treated patients exhibited higher plasma insulin levels and were more insulin resistant as compared to first episode

drug nave schizophrenia patients and had higher BMI, WHR, and waist circumference values (P = 0.01). On the other hand, there were no significant differences in BMI, WHR, and waist circumference parameters in patients with schizophrenia who discontinued treatment (P > 0.05) as compared to antipsychotic treated patients.

Patients with schizophrenia who discontinued treatment showed much higher plasma insulin resistance and more insulin resistance (P = 0.05) and higher BMI and waist circumference values (P = 0.01) as compared with first-episode drug-naive schizophrenia patients.

From this study, it was clear that weight gain, waist circumferences, and an increase in body mass index are closely related to the impairment of glucose metabolism and the incidence of insulin resistance regardless of the discontinuation of antipsychotic medication. Although these data have limitations, they should be interpreted and considered with caution because the author did not consider the associated modifiable risk factors of metabolic irregularities such as smoking, exercise, alcohol, and diet when analyzing the data. Furthermore, the nature of the study's being a cross-sectional design did not allow us to draw specific conclusions about causality. The study also had a small sample size, so it’s difficult to establish exactly what differences existed between the treated patients and those patients who discontinued treatments.

A study by Gautam and Meena (2011), which was done at the Psychiatric Centre, Jaipur, India, with the title "Drug Emergent Metabolic Syndromes in Patients with Schizophrenia Receiving Atypical Antipsychotics". It was a prospective study aimed at evaluating the occurrence of metabolic syndrome in psychiatric patients receiving atypical antipsychotics as compared to conventional antipsychotics. 120 patients with the diagnosis of schizophrenia were enrolled in this study and divided into 4 groups; 3 sub-treatment groups and one control, each having a total of 30 patients.

Apart from the ICD 10 diagnostic criteria, this study recruited only patients who were physically fit without any other physical or psychiatric illnesses. All patients had their blood pressure, fasting blood glucose, fasting triglycerides, fasting high-density lipoprotein, and waist circumferences measured. All these patients had either

never been treated with antipsychotics or were free from any antipsychotics for the past 6 months before the beginning of the study. 90 patients were given second-generation antipsychotics (risperidone, olanzapine, and clozapine) in their three respective groups of 30 patients each, and the remaining thirty were given conventional antipsychotics (haloperidol) as the control group. All four groups were observed for four months. The measurement parameters were repeated after one month of the treatment and at the end of four months.

After a 4-month treatment period, the study findings revealed no patients developed metabolic syndrome from the group of patients who were treated with conventional antipsychotics, though 11.66% of the study population developed metabolic derangements, and all of them were from those three groups who were given second-generation antipsychotics: 23.3% were treated with olanzapine, 10% risperidone, and 13% clozapine. A significant rise in fasting sugar levels was found in patients treated with clozapine and olanzapine.

Similarly, all patients in all four treatment groups showed significant weight gain; however, the maximum effect was seen in the Olanzapine and Clozapine groups, respectively. This effect of gaining weight was found to be directly related to the consequences of antipsychotics on appetite, body activities, and fasting blood glucose, which influence metabolic derangement and insulin sensitivity in the patients using them.

From the study findings, we further learned that Olanzapine is associated with the maximum outcome of weight gain and other metabolic irregularities among second-generation antipsychotics. However, no one of these three drugs was left behind.

The study concluded that second-generation antipsychotics have the highest risk of metabolic irregularities when compared to conventional antipsychotics and that both schizophrenic patients and those who have been off antipsychotics for the last 6 months have an equal chance of developing any form of metabolic syndrome, even though schizophrenia has no relationship with metabolic syndromes. Furthermore, Kim *et al., (*2010) in their study titled "Relationship between Body Mass Index and Insulin Resistance in Patients Treated with Second-Generation Antipsychotic Agents" found a similarly strong relationship between increasing body mass index

and rising steady-state plasma glucose concentration in patients with schizophrenia treated with second-generation antipsychotics for 4 months when compared with the large non-diabetic reference population. However, they further concluded that an atypical antipsychotic effect on insulin resistance is not unique to patients with schizophrenia.

Another study by Teff *et al.,* (2013), was done in Pennsylvania, Philadelphia, under the title "Antipsychotic Induced Insulin Resistance and Postprandial Hormonal Dysregulation Independent of Weight Gain or Psychiatric Disease". This was an experimental study with the overall objective of assessing the occurrence of the glucose metabolic consequences following second-generation antipsychotics in the absence of weight gain. It recruited 30 healthy individuals, who were divided into three subgroups: 2 treatment groups and one placebo, in a well-preserved hospitalized environment without limiting the participants' daily normal physical activities, and administered euglycemic hyperinsulinemic clamp and meal challenge aimed at evaluating the sensitivity of insulin and glucose disposal.

After 9 days of the intervention, it was found that there were no important variations in glucose metabolic parameters between the participants who were given antipsychotics, both olanzapine and aripiprazole, as compared to the placebo group. However, there were significant increases in serum fasting plasma insulin levels in the olanzapine group ($P = 0.05$).

The results further demonstrated no significant finding in a change of weight in all three subgroups before and post-intervention, though a mild, non-significant decrease in weight was noted in the aripiprazole group ($P = 0.008$), which may be explained as a result of some demographic data and not the effect of the drug given. However, there was an important finding in the data of decreasing insulin sensitivity and glucose disposal in both the olanzapine and the aripiprazole groups, respectively, as compared to placebo. The decreased finding of both glucose disposal and insulin sensitivity indicates the presence of insulin resistance in both individual groups kept on olanzapine and aripiprazole. Finally, we learned that the insulin resistance that was observed in this study was not directly correlated with the effect of olanzapine on adiposity and hyperlipidemia.

Another similar study by Gupta *et al.,(*2014) with the title "Metabolic Issues in Schizophrenic Patients Receiving Antipsychotic Treatments". This was carried out at the psychiatric center of SMS Medical College and its affiliated hospitals in 2013. It involved 210 in-and-out patients with ICD-10 diagnostic criteria for schizophrenia. They were free from any other diseases and free from drugs for the last 3 months before the beginning of this study.

The patients were divided into seven treatment groups each with 30 participants, 7 atypical antipsychotics, and one conventional drug was studied. Each group was given the drugs in a varied therapeutic dose regimen and kept on observation for 16 weeks after initiation of treatments. After this period of treatment blood investigation for the metabolic test was done, and anthropometric measurements were taken in all treatment groups with all seven-second generation antipsychotics and one atypical antipsychotic.

From this study, a significant weight change was observed in all seven groups with the patients treated with second-generation antipsychotics like olanzapine, clozapine, risperidone, and quetiapine though aripiprazole and amisulpride remained neutral without any weight change, at the same time olanzapine and clozapine resulted in a significant increase in waist circumference in all seven treatment groups. Neither weight gain nor increased weight circumferences were marked in patients who were treated with conventional antipsychotic haloperidol.

The results further demonstrated a marked rise in serum glucose level in all second-generation treated patients with exception of those who were given aripiprazole and amisulpride, similarly, serum insulin was higher in olanzapine, quetiapine, and clozapine treated patients.

Another study was done by (Nielsen, Skadhede, and Correll, 2010) in Denmark with the title of "Antipsychotic Associated with the Development of Type 2 Diabetes in Antipsychotic Naïve Schizophrenia patients". This was a ten years very big cohort study with the main objective of determining which antipsychotics are associated with the development of diabetes in inpatients with Schizophrenia starting antipsychotic medications for the first time. The study involved only patients with ICD 10 diagnostic criteria for Schizophrenia at the first time of diagnosis between

January 1997 to December 2007 and treated with antipsychotic medications for the first time. It also excluded all patients who had diabetes before the start of antipsychotic medications, and any other psychotic illness before the beginning of the study.

The treatment was divided into two major groups: those patients treated with conventional antipsychotics and those who were treated with atypical antipsychotics. Following the initiation of antipsychotics, the patients were followed up for at least three years, with compliance of at least one year in a group of specific antipsychotics.

The study ended with a total of 7,139 patients with schizophrenia who were free from diabetes at the time of the initiation of antipsychotic medications. Out of those, 307 developed diabetes during the follow-up period. The study findings explained that for those patients who developed diabetes earlier, most of them had advanced age and had been on second-generation antipsychotics for at least 3 months before the onset of the disease.

We also learned some discrepancies in this study regarding the antipsychotics that were described as associated with the occurrence of diabetes mellitus. They were treated with high-risk metabolic antipsychotics like Olanzapine and Clozapine, which were related to the weight gain that persisted in some of these patients throughout the study and had a strong correlation with the development of insulin resistance before the onset of diabetes in these patients. However, there were also a few patients who developed diabetes without being treated with second-generation antipsychotics or higher-risk metabolic antipsychotics.

These results further demonstrated that there were some second-generation antipsychotics like aripiprazole that had a very minimal risk of these metabolic irregularities, though these results should be considered with caution due to the limitations of this study, which include its lack of studying and analyzing other factors that could affect the risk of this disease, like the familial history of diabetes and other modifiable life factors such as physical inactivity, dietary habits of an individual, and body morphology.

Furthermore, the results did not give any information on changes in the prescription regimen, changes in the drugs among the patients, there was no information on the severity of the illness and adherence to drugs to either patient and at the same time, there was no control group where the outcome could be compared.

Finally, the nature of the study and screening procedures may have favoured drugs with high metabolic risks, such as clozapine, due to the necessity of emphasizing hematological monitoring to patients when starting with this drug and this may have influenced the early detection of metabolic consequences of these drugs in comparison to those with low metabolic risks.

A study by Newcomer *et al.,* (2009) (D, 2011) with the title "A 24-week multicentre open-label randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, and risperidone". In this study, 58 participating centers were involved from nine different countries across the world, with eight centers in South Africa. The main objective of this study was to compare differential changes in glucose metabolism, plasma lipids, and weight-related measures in patients with schizophrenia receiving olanzapine, quetiapine, or risperidone. A total of 574 patients were recruited in the study from 29 April 2004 to 24 October 2005, 510 out of 574 patients enrolled in the study with DSM IV criteria for the diagnosis of Schizophrenia aged from 18 to 64years, free from diabetes or using antidiabetic drugs and no history of using second-generation antipsychotic for three months before the beginning of the study were randomly categorized into groups regarding with their body mass index with equal opportunities of receiving any of the three antipsychotics which are olanzapine, risperidone and quetiapine, after randomization and five days of washout, they were given antipsychotic up to a maximum therapeutic dose of each drug an individual randomized for 24weeks without any other drugs with exception of benzodiazepine and some sleep medications.

After 24 weeks of treatment anthropometric measurements including weight and waist circumferences were checked, an oral glucose tolerance test was done and other additional glucose and lipid parameters were checked and compared between the groups.

The result of the study showed a marked increase in body weight in all three treatment group groups after 24 weeks of treatment and a maximum change in weight was found in the patients treated with olanzapine as compared to other groups. However, the study findings revealed a weak relationship between the change in body weight and its relationship with the change in insulin sensitivity or glucose tolerance.

After 24 weeks of treatment maximum decrease in glucose tolerance was observed in the patients treated with olanzapine as compared to quetiapine and Risperidone and this change was closely related to the decrease in insulin sensitivity

However, the interpretation of the results of this study has some limitation which has to be put into consideration and necessitate further discussion while interpreting it, first all patients were exposed to some antipsychotics and hence there was no control group where comparison concerning the outcome of the certain drug could be done. It also involved the patients who had been chronically treated with some antipsychotic medication and some of them received previous antipsychotics (typical) which all would have some effects on glucose metabolism, it involved the European population whose baseline weight and BMI might be higher which may affect the interpretation of the results.

Most of the studies however, were focused on western countries with advanced living standard and well developed health care system, and involved patients who were mostly exposed to most efficacious and notorious drugs with an increased risk of glucose metabolism impairments, while most patients in sub-Saharan African are on conventional antipsychotics and few afford atypical antipsychotic drugs. Saloojee et al., (2018), conducted a 12 months longitudinal study to assess the metabolic effects of antipsychotic drugs in drug naïve patients with psychotic disorders in South Africa and found the prevalence of 4.5% and incidence of 5.5% respectively with significant rise in waist circumferences following twelve months period of treatment with antipsychotic medications. The low prevalence and incidence in this study gave an assumption that may be black ethnicity are less likely to exhibit metabolic impairment compared to white (Saloojee, Burns and Motala, 2018), or as a result of miss diagnosis because of lack of regular screening of the problems.

CHAPTER THREE

3.0 Overview

This chapter will give an explanation of the research methods and techniques that were used to collect and analyze the data of this study.

3.1 Methodology

3.1.1 Study design.

This was a cross-sectional descriptive study aimed at optimizing the early diagnosis of glucose metabolism impairment in the adult population with psychiatric disorders attending an outpatient psychiatric clinic of the University Teaching Hospital in Lusaka, Zambia.

3.1.2 Study location.

The study was conducted at the psychiatric outpatient clinic of the University Teaching Hospital in Lusaka. This is the tertiary level hospital that is located in the capital city of the country. It is the largest public catchment specialized clinic in the country.

3.1.3 Target population.

The study was targeted at patients who were attending an outpatient psychiatric clinic at the University Teaching Hospital in Lusaka, Zambia from June to September 2021.

3.1.4 Study population.

All patients who were receiving antipsychotic medications, both first and second-generation antipsychotics, and who were on treatment for three months or more were screened for eligibility to participate in this study.

3.1.5 Sample size calculation.

The sample size calculation was computed by the following formula:-

$$N = \frac{Z^2 P (1-P)}{e^2}$$

Where: N = Sample size

Z = 1.96 standardized normal deviate for 95% confident interval

P = prevalence of patients with glucose metabolism impairments in previous study which was 6.2% = 0.062

e = maximum error allowed (5%)

$$N = \frac{(1.96)^2 (0.062) (1 - 0.062)}{(0.05)} = 90.$$

The minimum size required by using the above formula was 90.

3.1.6 Sampling technique.

A random systematic sampling technique was used to select the participants for this study. An estimated 160 patients were attending the outpatient psychiatric clinic at the University Teaching Hospital every month. This means the sampling interval was computed by 160/90 = 1.77. Therefore, every second patient on antipsychotic drugs was picked and screened for the inclusion criteria to participate in the study until the sample size was archived.

3.1.7 Inclusion criteria

The study included all patients with the following criteria

Patients taking antipsychotic medications, (both first and second-generation antipsychotics), for duration of three months and above with no history of diabetes or other health conditions that interfere with glucose metabolism.

3.1.8 Exclusion criteria.

All patients with diabetes mellitus (regarding information from past medical history of the participants), patients with family history of diabetes, patients on glucose-lowering drugs, patients on mood stabilizers, patients who were pregnant during the study period, patients who did not provide an informed consent and patients on long-term steroid medication were excluded from the study.

3.1.9. Study procedures.

A systematic random sampling technique was used to select participants who were attending an outpatient psychiatric clinic. The selected individuals who met the

required inclusion criteria were given an inclusion number and were recorded on an individual questionnaire. The researcher or research assistant explained the nature and aim of the study to every person who participated in the study. Consent forms were provided to the patients, who agreed to participate in the study, and they were requested to sign, and for those who were not be able to write were requested to sign using their thumbs and ink.

The nurses at the psychiatric clinic who were research assistants on the day of recruitment screened the patients for inclusion criteria, those who met the abovementioned criteria were tested for their random blood sugars and checked for their anthropometric measurements including weight, height, waist circumference, and estimation of body mass index of individual participants were calculated by weight against their height in square meters, then the results were recorded in the participant questionnaire.

The participants were allowed to go home and were instructed to come back the next day for testing of fasting blood sugar (FBS) while fasting for at least 8 hours. FBS was checked on the morning of the test before the patients take their breakfast. Results of fasting blood glucose were recorded in an individual participant questionnaire and the interpretations were performed using American Diabetic Association criteria.

3.1.10. Data collection tools.

For each participant in the study, data were collected using a patient structured questionnaire.

3.1.11. Data management, entry and analysis

Participants' information obtained was collected using a structured questionnaire. At the end of each participant's screening, the completeness and consistency of the questionnaires were checked. The data obtained was stored by the principal investigator in a well-secured environment. The correctly completed questionnaires were considered for analysis. Data entry, clearing, and analysis were done by the principal investigator using the Statistical Package for Social Science (SPSS) version 20.

Descriptive statistics were conducted to generate frequency tables of relevant variables, and cross-tabulations were conducted to explore the association between dependent and independent variables. Fisher's exact test was used to assess the associations involving the categorical variables. A P-value of less than or equal to 0.05 was considered to be statistically significant in the association being examined.

3.1.12. Dissemination of Data.

The data obtained from this study will be stored at the University of Zambia Medical Library for academic purposes and presented to the Department of Psychiatry of the University Teaching Hospital and the University Teaching Hospital management team. It will be disseminated to The Zambian Medical Journal, where a large number of health professionals will have access to read the information. It will also be presented to international scientific journals and conferences should the opportunity to do so arise.

3.1.13. Ethical clearance and considerations

The research was conducted by observing several ethical considerations. Ethical clearance was sought from the University of Zambia Biomedical Research Ethics Committee (UNZABREC) and forwarded to the National Health Research Authority (NHRA) before the carrying out of the study. The participants' autonomy was observed accordingly. All participants were informed about the voluntary nature of the study and their freedom to withdraw at any stage without any consequences to them. All participants were made aware that the procedure of the study was basic screening, simple, and non-invasive, though it took some time and induced some discomfort, which was mild and tolerable to all of the participants.

The benefits of the study were clearly explained so that an individual would have known his or her glucose metabolic status, and for those individuals who needed medical help or advice was given appropriately. Permission to conduct the study was also granted by the head of the department of psychiatry.

All consent forms were provided in English, interpreted in the participant's local language, and all participants signed after reading, understanding, and agreeing to participate in the study.

Confidentiality was upheld during the whole period of the study, and each participant was given an inclusion number and assured that their names would not be used in the report or published where the publication of this study is necessary.

CHAPTER FOUR

4.0 Overview

This chapter presents the results of the study. The results of this study will be presented based on the main objective of the study which was to optimize the early diagnosis of glucose metabolism impairments in patients with psychotic disorders who were receiving antipsychotic medications. Specifically, the study was targeted to determine the demographic characteristics and proportion of patients with psychotic disorder who developed early glucose metabolism impairment when treated with antipsychotic medications, to determine the association between glucose metabolism impairment and type of antipsychotic medication used and finally to determine the relationship between the duration of antipsychotic medication use and development of glucose metabolism impairments.

4.1. Results

4.1.1. Demographic characteristics of the participants.

The first objective of this study was to determine the demographic characteristics and proportions of patients with psychotic disorder who developed early glucose metabolism impairment when receiving antipsychotic medications.

Table 1: Demographic characteristics of the study participants

Variable	Value	Frequency (N=90)	Percentage (%)
Age group	18-35	40	44.4
	36-55	29	32.2
	56+	21	23.3
Sex	Male	43	47.8
	Female	47	52.2
Diagnosis	Schizophrenia	62	68.88
	Other psychotic disorders	28	31.11
Body mass index	Normal(18.5-24.5Kg/m2)	43	47.8
	Over weight (25-29.5Kg/m2)	24	26.7
	Obese(30+Kg/m2)	13	14.4
	Low BMI(>18.5Kg/m2)	10	11.11
Waist circumference	Normal (if <80cm for women or <90cm for men)	55	61.1
	Increased (if > 80cm for women or > 90cm for men)	35	38.9
Types of antipsychotic used	Typical antipsychotics	24	26.7
	Atypical antipsychotics	51	56.7
	Both typical and atypical antipsychotics	15	16.7
Duration of treatments	Not more than three months	14	15.6
	Up to six months	29	32.2
	More than six months	47	52.2
Fasting blood glucose levels	Normal	71	78.9
	Impaired	09	10.0
	Diabetes	10	11.1
Blood pressure measurements	Normal BP(<140/90mmHg)	61	67.8
	High BP(>140/90mmHg)	29	32.2

In this study, a total of ninety 90 adult patients with psychotic disorders were enrolled for participation. Large numbers of participants 62(68.88%) were on

treatment with the diagnosis of schizophrenia and few 28(31.11%) were having other psychotic disorders. Forty-three (47.8%) of the participants were male while forty-seven (52.2%) were females. Forty (44.4%) were aged 18-35 years, 29 (32.2%) participants were aged 36-55 years, and 21 (23.3%) were aged 56 years and above.

Fourteen (15.6%) participants had been on antipsychotic medication for not more than three months, 29 (32.2%) participants had been on antipsychotic medication up to six months, and 47 (52.2%) had been on antipsychotic medication for more than six months.

Further analysis revealed that 24 (26.7%) participants were taking typical antipsychotic medication, 51 (56.7%) participants were taking atypical antipsychotic medication, and 15 (16.7%) were taking both typical and antipsychotic medication. Lastly, the results revealed that 61(67.8%) participants had normal blood pressure while 29 (32.2%) had high blood pressure.

4.1.2. Proportion of fasting blood glucose levels among the study participants

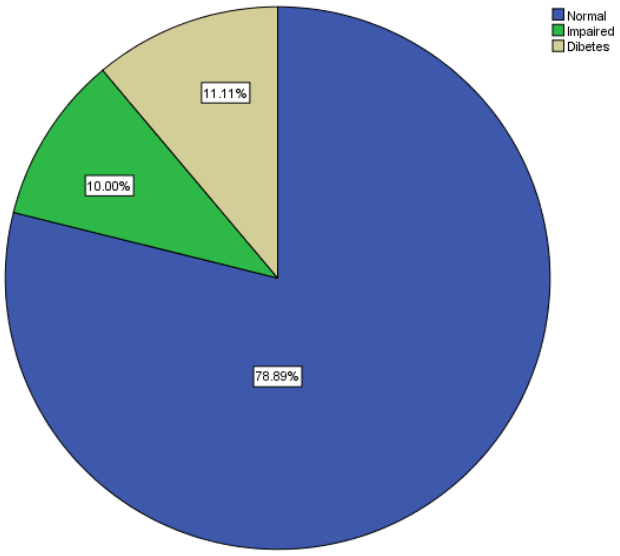

Fig 1a, Showing the proportion of fasting blood glucose levels among the study participants.

The participants were tested to establish their fasting blood glucose. Seventy-one (78.9%) participants' fasting blood glucose was normal, 9 (10.0%) participants' fasting blood glucose was impaired and 10(11.1%) met the criteria for diabetes mellitus.

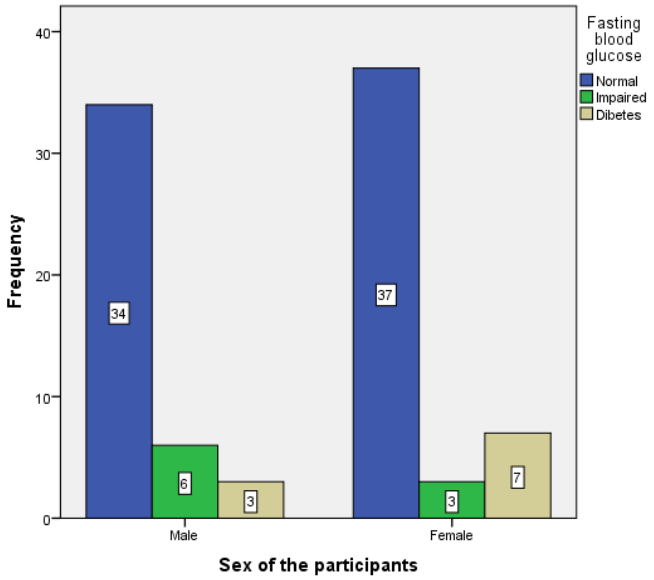

Fig 1b, Showing the proportion of fasting blood glucose by sex of the participants

The proportion of impaired fasting blood glucose was higher among male patients 6(6.67%) than female 3(3.33%) where the proportion diabetes was higher in female 7(7.78%) than male 3(3.33%), the differences were statistically non-significant χ^2 (2, n = 90) = 2.455, p = 0.333.

4.1.3. Proportion of fasting blood glucose levels by age of the participants

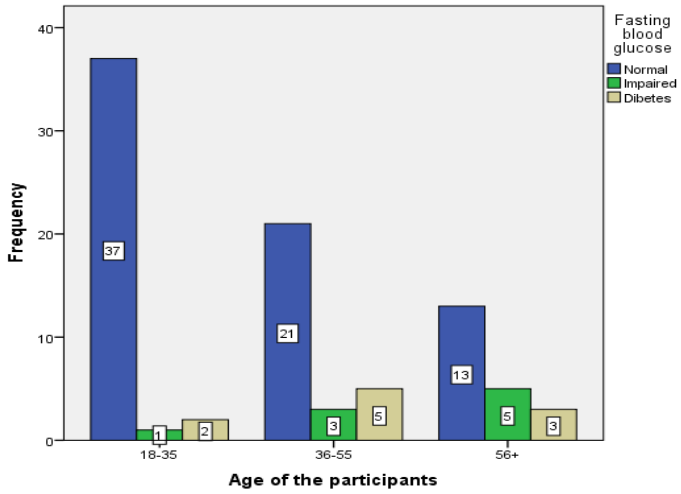

Fig 2, Show the relationship between age and levels of fasting blood glucose among the study participants

In this study it was found that, patients aged 36 and above had higher level of impaired fasting blood glucose 5(5.56%) higher proportion of diabetes 5(5.56%), these results were statistically significant χ^2 =10.323, p-value=0.020.

4.1.4 Relationship between waist circumference and fasting blood glucose level

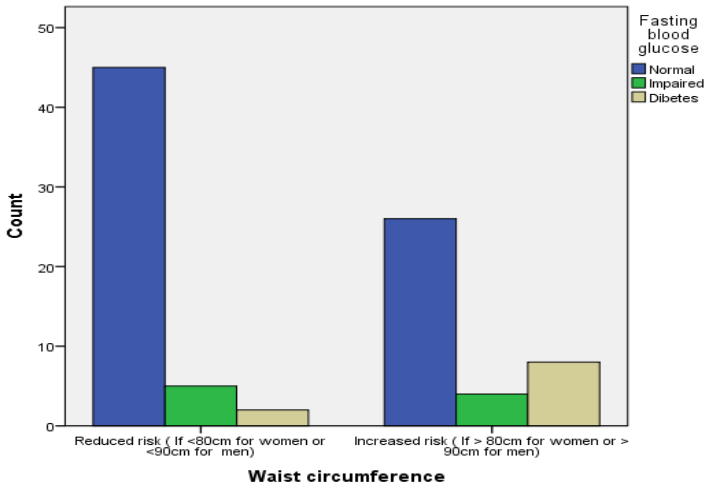

Fig 3, showing the proportion of fasting blood glucose levels in relation to the waist circumferences of the study participants

A Fishers Exact test was performed to examine a relation between waist circumference (WC) and fast blood glucose (FBG), at a significance level of 0.05. The relation between the two variables was significant, χ^2 (2, n = 90) = 6.612, p = .030. Participants who had higher waist circumference were more likely to have impaired fasting blood glucose levels and diabetic.

4.1.5 Association between fasting blood glucose levels and type of antipsychotic medications used.

The second objective of this study was to determine the association between glucose metabolism impairment and the type of antipsychotic medication used. A Fishers Exact test was performed to examine the association between the two variables at a significance level of 0.05. The relation between the two variables was significant, $\chi 2$ (4, n = 90) = 9.616, p = 0.029, see table 2a, fig 2a below. Patients who were taking atypical antipsychotic medication were more likely to be diabetic, while patients who

were taking both atypical and typical antipsychotic medications were more likely to be impaired than those who were taking typical antipsychotic medication alone.

Table 2, Relationship between types of antipsychotic medications used and fasting blood glucose levels.

	Fasting blood glucose				χ^2	**P-value**
	Normal, N (%)	**Impaired, N (%)**	**Diabetes, N (%)**	**Total, N (%)**		
Typical antipsychotics	21(23.33)	02(2.22)	02(2.22)	25(27.78)		
Atypical antipsychotics	38(42.22)	02(02.22)	08(8.89)	48(53.33)	9.614	0.029
Both typical and atypical antipsychotics	12(13.33)	05(5.56)	00(0.00)	17(18.89)		
Total	71(78.89)	09(10.00)	10(11.11)	90(100)		

Table 2, showing relationship between types of antipsychotic used and levels of fasting blood glucose impairments.

In this study, a large percent 8.89% of patients who met the criteria for the diagnosis of diabetes mellitus were using second-generation antipsychotic compared to 2.22% who met the same diagnostic criteria were using first-generation antipsychotic (χ^2 =9.614, p – value 0.029)

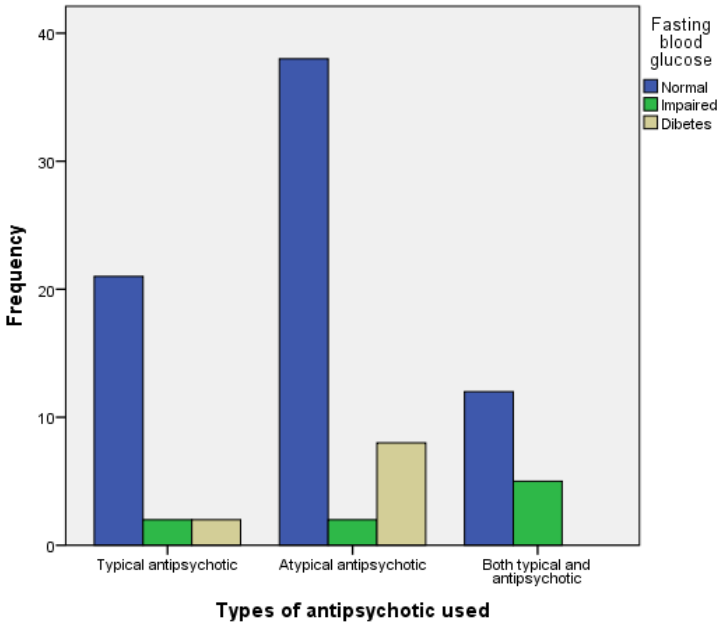

Fig 4a, Showing the type of antipsychotic used by the patients and levels of fasting blood glucose

In this study it was found that patients who were using atypical antipsychotic medications and combination of both typical and atypical antipsychotics were more likely to have impaired blood fasting blood glucose levels and to be diabetes compared to the one who were taking first generation antipsychotic medications alone, the differences was statistically significant χ^2 (4, n = 90) = 9.616, p = 0.029.

4.1.6. Relationship between duration of antipsychotic use and fasting blood glucose levels

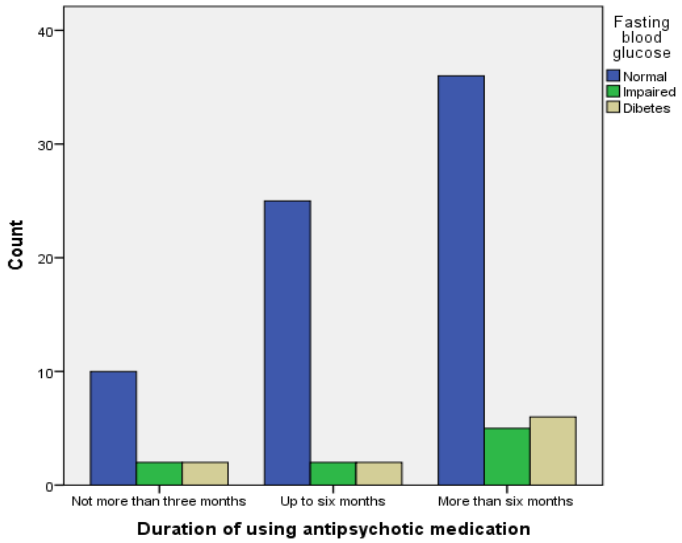

Fig 4b, showing the duration of antipsychotic use in relation to the fasting blood glucose levels among the study participants.

Patients taking antipsychotic medication for more than six months period duration exhibited higher proportion of impaired fasting blood glucose level as well as had higher proportion of diabetes compared to those who were on medication for less than six months period. Fisher's exact test was performed to examine a relation between duration of using antipsychotic medication and fasting blood glucose (FBG), at a significance level of 0.05. The relation between the two variables was not significant, χ^2 (4, n = 90) = 1.930, p = 0.792.

CHAPTER FIVE

5.0 An overview

This is the first kind of study to be conducted at Clinic Six, Department of Psychiatry at the University Teaching Hospital. The study used simple and basic screening methods aimed at optimizing the early diagnosis of glucose metabolism impairment for patients with psychiatric disorders who were receiving antipsychotic medications at the outpatient psychiatric clinic of the University Teaching Hospital in Lusaka. Specifically, this study described the demographic characteristics and proportion of patients with glucose metabolism impairment who were receiving antipsychotic medications. It also described the relationship between glucose metabolism impairment and the types of antipsychotic medications used. The focus on glucose metabolism impairments was given special consideration because it is closely associated with other medical conditions such as cardiometabolic disease and its related co-comorbid conditions, which worsen psychiatric treatment and outcome.

5.1. Summary of the results

In this study, it was found that a large proportion of the participants were aged between 18-35 years which was Forty (44.4%) and a smaller proportion of 21 (23.3%) were aged 55 years and above. Among all participants 24 (26.7%) were taking typical antipsychotic medications, 51 (56.7%) atypical antipsychotics, and 15 (16.7%) were taking both typical and atypical antipsychotic medications at the same time. 11.11% were underweight, 26.7% overweight and 14.4% were obese, while 38.9% had higher waist circumferences. Increased in age were associated with impaired fasting blood glucose levels and diabetes χ^2 (4, n = 90) = 10.323, p = 0.022. A Fishers Exact test was performed to examine the relation between Body Mass Index (BMI) and fasting blood glucose levels (FBG), at a significance level of 0.05. The relation between the two variables was not significant, χ^2 (6, n = 90) = 3.691, p = 0.730. However increase in waist circumferences was highly associated with impaired fasting glucose levels χ^2 (2, n = 90) = 6.612, p = 0.030. The overall proportion of impaired fasting blood glucose levels was 10% and diabetes at 11.1%, female participants had a higher proportion compared to males though statistically

were nonsignificant χ^2 (2, n = 90) = 2.455, p = 0.333. Second-generation antipsychotics were highly associated with impaired fasting blood glucose levels and diabetes. Duration of antipsychotic medication use was not associated with the development of impaired fasting blood glucose levels (FBG), χ^2 (4, n = 90) = 1.930, p = 0.792.

5.1.1. Demographic characteristics of the study participants

The demographic features of the study participants revealed that there were more females than males attending outpatient psychiatric clinic services during the study period. These findings are consistent with the study done by Nyoni *et al.,* (2018) in Zimbabwe, who found that the percentage of female (69.4%) participants was higher compared to males. The same findings of a higher percentage of females (55.63%) were seen in a study which was done in Uganda to determine the prevalence of metabolic syndrome in patients with psychiatric disorders (Agaba *et al.,* 2019). This could be owing to the perception that females are more likely to seek medical help than males. In terms of body mass index, 14.4% and 26.7% of the participants were obese and overweight, respectively. Although females were more likely to have a higher percentage of overweight than males, statistically, this was not significant. This finding does differ from the one that was found in a study done by Edith Kwobah and colleagues, which showed that 45% of the patients with a psychiatric disorder were obese as compared to normal individuals who were not suffering from psychotic disorders (Kwobah *et al.,* 2021). In terms of waist circumferences, 42.2% of the study population had higher waist circumferences. Female participants also had a higher proportion as compared to male participants, but this was statistically not significant. However, this result again is similar to the one which was found in patients with psychotic disorder who exhibited higher waist circumference than control in a study which was conducted in Kenya (Kwobah *et al.,* 2021).

5.1.2. Proportion of glucose metabolism impairments among the study participants

Patients receiving antipsychotic medication are significantly at risk of developing glucose metabolism impairment compared to the general population. The overall proportion of impaired fasting blood glucose found in this study was 10% and

diabetes was 11.1%, respectively. These results are higher compared to one observed in the general Zambian population as reported in a study by Nsakashalo-Senkwe and colleagues, who reported a prevalence of impaired glucose levels of 4.0% in the general Zambian population (Nsakashalo-Senkwe *et al.*, 2011). Mwila and colleagues reported a prevalence of diabetes type 2 of 2.1% among men and 3.0% among women, based on a population survey study that was conducted in 2012 in the Zambian general population as well (Mwila, Bwembya, and Jacobs, 2019). It is also contrary to the one that was reported in Ethiopia by Daniel et al., in a study that was aimed to determine the prevalence of undiagnosed diabetic Mellitus among patients with psychiatric disorders in Ethiopia. In this Ethiopian study, 7.3% of the patients with psychiatric disorders met the standard diagnostic criteria set by the World Health Organization (WHO) for the diagnosis of diabetes type 2, which was also higher compared to that found in the general population (Daniel *et al.*, 2017).

However, the finding of this study is in line with other studies which were conducted in a different part of the world. Olsson *et al.*, 2015 did a study in Sweden to evaluate the prevalence of diabetes and prediabetes in patients with psychosis and found the prevalence of 10% and 10% respectively (Olsson *et al.*, 2015). Wani and colleagues did a study in India and found the prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia was 16.0% and 30.9% respectively (Wani *et al.*, 2019). These results are higher compared to the one which was found in Zambia, differences in environmental exposures and standard of life exhibited by these two different nations could be the reason for this discrepancy.

The results of this study also found that patients who were 55 years and older showed a higher proportion of diabetes compared to the younger ones, which was statistically significant ($p = 0.022$). This should be an alarm to psychiatrists and other health professionals working in psychiatric settings, as degenerative changes that occur with aging could be another risk factor of glucose metabolism impairment in conjunction with antipsychotic medications, though this finding contradicts the one reported in a study by Whicher and colleagues that reported young adolescent exhibited higher levels of impaired glucose tolerance and at higher risk of diabetes than adults when starting treatment with antipsychotic medications. Another important observation that was found in this study is that an increase in waist circumference was significantly associated with impaired fasting blood glucose levels (P-value = 0.030).

However, there were a small proportion of the participants with low waist circumference and even low BMI who also demonstrated some degree of impaired fasting blood glucose and some met the criteria for the diagnosis of diabetes mellitus (table 1a). In this study, increasing body mass index was not significantly tested to be associated with glucose metabolism impairments.

On the other hand, sex was not a significant risk factor for glucose metabolism impairment, unlike the findings of another study like that was done by Daniel et al., in Ethiopia that reported female sex has a significant risk of impaired glucose metabolism including hyperglycemia and diabetes

5.1.3. Association between Glucose Metabolism impairment and type of antipsychotic medication use

The study's second objective was to determine if there was a link between impaired glucose metabolism and the type of antipsychotic drugs used. It was found that patients who received long-term treatment with the newer generation of antipsychotic drugs were more likely to have impaired fasting blood glucose levels and diabetes than those who received conventional antipsychotic medications alone, according to this study. This finding is in line with a meta-analysis study that demonstrated that patients with severe mental illnesses like schizophrenia who were treated with second-generation antipsychotics like olanzapine had significantly higher blood glucose levels than those who were on typical antipsychotics (Zhang *et al.,* 2017). It was also in line with the findings of a big study that compared the effects of eighteen different drugs which also concluded that those who were in the newer generation of antipsychotic medications had a higher proportion of glucose metabolism impairments compared to the conventional one (Pillinger *et al.*, 2020).

5.1.4. Relationship between duration of antipsychotic medications use and impairment of glucose metabolism

Patients with psychotic disorders who took antipsychotic medications for more than six months had a higher proportion of diabetes and impaired fasting blood glucose levels than those who were taking antipsychotic drugs for less than six months however, this difference, were not statistically significant. Thus the length of antipsychotic medication had no bearing on the findings of fasting blood glucose

levels that were impaired. This finding contradicts Daniel and colleagues (2017) finding's which found a substantial link between long-term antipsychotic usages to be linked to the development of undetected diabetes in a patient with psychotic illnesses (Daniel *et al.*, 2017).

CHAPTER SIX

6.0 Overview

This chapter will give highlight of the limitations of the study, conclusions and recommendation based on the results of the study.

6.1 Limitations

This study had some limitations which were of great concern; some were identified during the process of data collection and the time of data analysis and need to be addressed in future studies. The first study's limitation is the way the questionnaires were developed. It was not easy to capture other factors that could have had a potential contribution to glucose metabolism impairment, such as level of education, exercise pattern, social support, the living standard of particular participants, and dietary habits, which were not inquired into during the process of data collection. Since then, education has been regarded as the most important determinant of safe living when it comes to adopting healthy lifestyle choices. Thus, it is expected of a well-educated individual to adopt a healthy, safe lifestyle in terms of eating habits and physical exercise. Similarly, regular physical exercise is crucial for regulating and balancing glucose metabolism levels.

The study also involved a relatively small number of participants, so these results cannot be conclusively generalized to the total community of patients with psychiatric disorders in Zambia. This necessitates a further study which will involve a larger number of participants with the diversity of cases in both inpatient and outpatient services, which should be comprehensive and should inquire a lot of important information like the standard of living and lifestyle habits to give a true picture of the problem in the community.

Lastly, the study used a cross-sectional design that has an inherent weakness in evaluating the temporal relationship between exposure and outcomes. Although it gives an insight into the problem, it is difficult for the results to clearly show the direction of the association. Thus, there is a need for future researchers to conduct longitudinal studies looking at the association between specific antipsychotic drugs used and the development of glucose metabolism impairments.

6.2 Conclusion

The glucose metabolism deficit in patients with psychotic disorders was found to be high. Patients of both sexes, male and female, had an equal chance of developing the problem, though females had a higher proportion as compared to males, and it is not time-dependent. Older patients showed a higher proportion of impaired fasting blood glucose levels compared to younger ones. Increased waist circumferences were significantly associated with a higher proportion of impaired fasting blood glucose levels. Body mass index was statistically not significantly associated with impaired fasting blood glucose levels, although most patients who exhibited impaired fasting blood glucose levels were overweight or obese, there was a small proportion of patients who had low body mass index and yet exhibited impaired fasting blood glucose levels or diabetes. Patients who were taking second-generation antipsychotics were potentially shown to have a higher proportion of impaired glucose metabolism compared to those who were taking only typical antipsychotic medications.

6.3 Recommendations

It is recommended that basic screening measures of glucose metabolism parameters that are simple and cost-effective, like checking weight, BMI, waist circumferences and regular checking of blood glucose levels, be routine practice in all psychiatric settings before starting antipsychotic medications. Close monitoring of glucose metabolic parameters should be incorporated in a normal psychiatric practices especially when patients taking second generation antipsychotic medications. Appropriate measures should be taken for every patient who seems to be at higher risk. For those who are detected with the problem, adequate care should be given and the right choice of medication should be provided. Clinical knowledge on glucose metabolism impairments, their consequences, prevention, and management approach should be disseminated to every clients visiting to the psychiatric clinic.

Dietary advice and encouraging physical activities should be integrated into psychiatric practice. Education should also be aired every time patients come into contact with a psychiatric health facility, or even the media should be used to air out information concerning psychotic disorders and their related comorbid conditions

like glucose metabolism impairments. Another option for strengthening psychiatric services, especially for vulnerable patients, should be a multidisciplinary approach involving physicians and endocrinologists.

REFERENCES

Annamalai, A. and Tek, C. (2015) 'An overview of diabetes management in schizophrenia patients: Office based strategies for primary care practitioners and endocrinologists', International Journal of Endocrinology, 2015. doi: 10.1155/2015/969182.

Agaba, D. C. et al. (2019) 'Prevalence and Associated Factors of Metabolic Syndrome among Patients with Severe Mental Illness Attending a Tertiary Hospital in Southwest Uganda', BioMed Research International, 2019. doi: 10.1155/2019/1096201.

Aykut, D. S. and Karagüzel, E. Ö. (2018) 'A comparison of depot and oral atypical antipsychotics in terms of metabolic syndrome markers'. Taylor & Francis, 0573. doi: 10.1080/24750573.2017.1414575.

Bailey S. Lou, Helen Ayles, Nulda Beyers, Peter Godfrey-FaussettMonde Muyoyeta, Elizabeth du Toit, John S. Yudkin, Sian Floyd. (2016) 'Diabetes mellitus in Zambia and the Western Cape province of South Africa: Prevalence, risk factors, diagnosis and management', Diabetes Research and Clinical Practice. The Authors, 118, pp. 1–11. doi: 10.1016/j.diabres.2016.05.001.

Bobo, V. William O. Cooper, Michael Stein, Mark Olfson, David Graham, James Daugherty, Catherine Fuchs, Wayne A. Ray, (2013) 'Antipsychotics and the risk of type 2 diabetes mellitus in children and youth', JAMA Psychiatry, 70(10), pp. 1067–1075. doi: 10.1001/jamapsychiatry.2013.2053.

Boyda, H. N, Ric M. Procyshyn, Catherine C. Y. Pang, Erin Hawkes, Daniel Wong, Chen Helen Jin, William G. Honer, Alasdair M. Barr (2013) 'Metabolic Side-Effects of the Novel Second-Generation Antipsychotic Drugs Asenapine and Iloperidone: A Comparison with Olanzapine', PLoS ONE, 8(1), pp. 1–11. doi: 10.1371/journal.pone.0053459.

Burghardt, K. J. Jacyln M. Goodrich, Dana C. Dolinoy, Vicki L Ellingrod. (2016) 'specific DNA methylation may mediate atypical induced insulin resistance', (April), pp. 423–432. doi: 10.1111/bdi.12422.

Castellani, L. N., Kenya A. Costa-Dookhan, William B. McIntyre, David C. Wright, Stephanie A. Flowers, Margaret K. Hahn, Kristen M. Ward. (2019) 'Preclinical and Clinical Sex Differences in Antipsychotic-Induced Metabolic Disturbances: A Narrative Review of Adiposity and Glucose Metabolism', Journal of Psychiatry and Brain Science. doi: 10.20900/jpbs.20190013.

Chen, J., Xu-Feng Huang, Renfu Shao, Chen Chen and Chao Deng (2017) 'Molecular mechanisms of antipsychotic drug-induced diabetes', Frontiers in Neuroscience, 11(NOV), pp. 1–12. doi: 10.3389/fnins.2017.00643.

Cottingham, E. M., David J. Klein, Michael Sorter, Bruce A. Barton, John A. Morriso. (2006) 'Metformin Treatment of Weight Gain Associated With Initiation of Atypical Antipsychotic Therapy in Children and Adolescents', (Am J Psychiatry 2006; 163:2072–2079.

Daniel, Asmelash, Wondale Getnet, Belete Biadgo, Sintayehu Ambachew, Tadele Melak, Lemmesa Melese, Shiwaneh Damite, Habtamu Wondifraw Baynes, Molla Abebe. (2017) 'Undiagnosed Diabetes Mellitus and Associated Factors among Psychiatric Patients Receiving Antipsychotic Drugs at The University of Gondar Hospital , Northwest Ethiopia', pp. 3–10.

Dayabandara, M. *et al.* (2017) 'Antipsychotic-associated weight gain: Management strategies and impact on treatment adherence', *Neuropsychiatric Disease and Treatment*, 13, pp. 2231–2241. doi: 10.2147/NDT.S113099.

Dasgupta, A, Om Prakash Singh, Jayanta Kumar Rout, Tanmay Saha, Sonai Mandal (no date) 'Author ' s personal copy Progress in Neuro-Psychopharmacology & Biological Psychiatry Insulin resistance and metabolic pro fi le in antipsychotic naïve schizophrenia patients'. doi: 10.1016/j.pnpbp.2010.06.011.

Deng, C. (2013) 'Effects of antipsychotic medications on appetite, weight, and insulin resistance', 42, p. 8529.

Didier Meulien, John W. Newcomer, Robert E. Ratner, Jan W. Eriksson, Robin Emsley, , Frank Miller, Julia Leonova-Edlund, Ronald W Leong, and Martin Brecher (2011) "A 24-Week, Multicentre, Open-Label, Randomized Study To Compare Changes In Glucose Metabolism In Patients With Schizophrenia Receiving Treatment With Olanzapine, Quetiapine And Risperidone" NIH Public Access', *Bone*, 23(1), pp. 1–7. doi: 10.1161/CIRCULATIONAHA.110.956839.

Fleischhacker, W. W, Cynthia O. Siu, Robert Bode´n, Elizabeth Pappadopulos, Onur N. Karayal, Rene´ S. Kahn the EUFEST study group (2013) 'Metabolic risk factors in first-episode schizophrenia: Baseline prevalence and course analysed from the European First-Episode Schizophrenia Trial', International Journal of Neuropsychopharmacology, 16(5), pp. 987–995. doi: 10.1017/S1461145712001241.

Gautam, S. and Meena, P. S. (2011) 'Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics', Indian Journal of Psychiatry, 53(2), pp. 128–133. doi: 10.4103/0019-5545.82537.

Gupta, A, Gora Dadheech, Dharamveer Yadav, Praveen Sharma, Shiv Gautam. (2014) 'Metabolic issues in schizophrenic patients receiving antipsychotic treatment', Indian Journal of Clinical Biochemistry, 29(2), pp. 196–201. doi: 10.1007/s12291-013-0415-z.

Hammoudeh, S, Suhaila Ghuloum, Ziyad Mahfoud, Arij Yehya, Abdulmoneim Abdulhakam, Azza Al-Mujalli, Mahmoud Al-Zirie, Mohamed Osman Abdel Rahman, Angela Godwin, Noura Younes, Yahya Hani, Dennis Mook-Kanamori, Marjonneke Mook-Kanamori, Reem E Sherbiny, and Hassen Al-Amin (2018) 'The prevalence of metabolic syndrome in patients receiving antipsychotics in Qatar : a cross sectional comparative study'. BMC Psychiatry, pp. 1–9.

Houseknecht, K. L., Alan S Robertson, William Zavadoski, E Michael Gibbs, David E Johnson and Hans Rollema. (2007) 'Acute Effects of Atypical Antipsychotics on Whole-Body Insulin Resistance in Rats : Implications for Adverse Metabolic Effects', pp. 289–297. doi: 10.1038/sj.npp.1301209.

Ingimarsson, O. MacCabe J. Haraldsson M, Jónsdóttir H, Sigurdsson E. (2017) 'Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment of schizophrenia in Iceland', Nordic Journal of Psychiatry. Taylor and Francis Ltd, 71(7), pp. 496–502. doi: 10.1080/08039488.2017.1334821.

Inzucchi, S. E. et al. (2012) 'Management of hyperglycemia in type 2 diabetes: A patient-centered approach', Diabetes Care, 35(6), pp. 1364–1379. doi: 10.2337/dc12-0413.

Jeon, S. W. and Kim, Y. (2017) 'Unresolved Issues for Utilization of Atypical Antipsychotics in Schizophrenia : Antipsychotic Polypharmacy and Metabolic Syndrome'. doi: 10.3390/ijms18102174.

Kaushal, J., Bhutani, G. and Gupta, R. (2012) 'Comparison of fasting blood sugar and serum lipid profile changes after treatment with atypical antipsychotics olanzapine and risperidone', 53(7), pp. 488–492.

Kowalchuk, C. et al. (2019) 'Antipsychotics and glucose metabolism: How brain and body collide', American Journal of Physiology - Endocrinology and Metabolism, 316(1), pp. E1–E15. doi: 10.1152/ajpendo.00164.2018.

Kwobah, E. et al. (2021) 'Prevalence and correlates of metabolic syndrome and its components in adults with psychotic disorders in Eldoret, Kenya', PLoS ONE, 16(1 January), pp. 1–15. doi: 10.1371/journal.pone.0245086.

Krhač, M. and Lovrenčić, M. V. (2019) 'Update on biomarkers of glycemic control', World Journal of Diabetes, 10(1), pp. 1–15. doi: 10.4239/wjd.v10.i1.1.

Li,Ranran, Jianjun Ou , Li Li , Ye Yang , Jingping Zhao and Renrong Wu. (2018) 'The Wnt Signaling Pathway Effector TCF7L2 Mediates Olanzapine-Induced Weight Gain and Insulin Resistance', 9(April), pp. 1–13. doi: 10.3389/fphar.2018.00379.

Lipscombe, L. L., Peter C. Austin, Silvia Alessi-Severini, David F. Blackburn, Lucie Blais. (2014) 'Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data', Schizophrenia Research. The Authors, 154(1–3), pp. 54–60. doi: 10.1016/j.schres.2014.01.043.

Luo, C., Xu Wang, Hanxue Huang , Xiaoyuan Mao , Honghao Zhou and Zhaoqian Liu. (2019) 'Effect of metformin on antipsychotic-induced metabolic dysfunction: The potential role of gut-brain axis', Frontiers in Pharmacology, 10(APR), pp. 1–8. doi: 10.3389/fphar.2019.00371.

Martins, P. J. F., Haas, M. and Obici, S. (2010) 'Central Nervous System Delivery of the Antipsychotic Olanzapine Induces Hepatic Insulin Resistance', 59(October). doi: 10.2337/db10-0449.

Melkersson, K., Berinder, K. and Hulting, A. L. (2011) 'Effect of antipsychotic-induced hyperprolactinemia on anthropometric measures, insulin sensitivity and lipid profile in patients with schizophrenia or related psychoses', Neuroendocrinology Letters, 32(4), pp. 428–436.

Mhatre V. Ho and Kelsey C. Martin, J.-A. L. (2012) 'NIH Public Access', Bone, 23(1), pp. 1–7. doi: 10.1016/j.molmed.2010.10.010.Antipsychotic.

Nanasawa, H. , Akahito Sako, Tomohiko Mitsutsuka, Kaori Nonogaki, Tadayuki Kondo, Shuichi Mishima, Yoriyasu Uju, Toshihiko Ito, Tetsuro Enomoto, Tatsuro Hayakawa, Hidekatsu Yanai, (2017) 'Development of diabetes mellitus associated with quetiapine', 0(December 2016).

Nielsen, J., Skadhede, S. and Correll, C. U. (2010) 'Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients', Neuropsychopharmacology, 35(9), pp. 1997–2004. doi: 10.1038/npp.2010.78.

Nsakashalo-Senkwe, M., Seter Siziya, Fastone M Goma, Peter Songolo, Victor Mukonka1, Olusegun Babaniyi (2011) 'Combined prevalence of impaired glucose level or diabetes and its correlates in Lusaka urban district, Zambia: A population based survey', International Archives of Medicine. BioMed Central Ltd, 4(1), p. 2. doi: 10.1186/1755-7682-4-2.

Olsson, E., Jeanette Westman, Dzana Sudic Hukic, Sven V Eriksson, Gunnar Edman, Robert Bodén, Erik Jedenius, Johan Reutfors, Anders Berntsson, Agneta Hilding, Martin Schalling, Claes-Göran Östenson, Urban Ösby. (2015) 'Diabetes and glucose disturbances in patients with psychosis in Sweden', pp. 1–8. doi: 10.1136/bmjdrc-2015-000120.

Owusu-Ansah, A., Anto Berko Panyin, Christian Obirikorang, Christian Agyare , Emmanuel Acheampong , Simon Kwofie, Enoch Odame Anto , and Emmanuella Nsenbah Batu. (2018) 'Metabolic syndrome among schizophrenic patients: A comparative cross-sectional study in the middle belt of Ghana', Schizophrenia Research and Treatment, 2018. doi: 10.1155/2018/6542983.

Panagiotopoulos, C., Ronsley, R. and Davidson, J. (2009) 'Increased Prevalence of Obesity and Glucose Antipsychotic Medications', The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie, 54(11), pp. 743–749.

Phir, M., David Mulenga, Mazyanga L Mazaba, Seter Siziya. (2016) 'Prevalence of Diabetes mellitus and association between knowledge of diabetes and Diabetes mellitus among police officers in Peter Singogo camp, Zambia', Asian Pacific Journal of Health Sciences, 3(3), pp. 87–89. doi: 10.21276/apjhs.2016.3.3.14.

Pillinger, T. et al. (2020) 'Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis', The Lancet Psychiatry. The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license, 7(1), pp. 64–77. doi: 10.1016/S2215-0366(19)30416-X.

Riordan, H. J., Antonini, P. and Murphy, M. F. (2011) 'Atypical antipsychotics and metabolic syndrome in patients with schizophrenia: Risk factors, monitoring, and healthcare implications', American Health and Drug Benefits, 4(5), pp. 292–302.

Saloojee, S., Burns, J. K. and Motala, A. A. (2018) 'Metabolic syndrome in antipsychotic naive African patients with severe mental illness in usual care', *Early Intervention in Psychiatry*, 12(6), pp. 1137–1143. doi: 10.1111/eip.12428.

Santini, I., Paolo Stratta, Simona D'onofrio, Ida De Lauretis, Valeria Santarelli, Francesca Pacitti, Alessandro Rossi (2016) 'The metabolic syndrome in an Italian psychiatric sample : a retrospective chart review of inpatients treated with antipsychotics', 51(1), pp. 37–42.

Sliwa, J. K., Dong-Jing Fu, Cynthia A Bossie, Ibrahim Turkoz and Larry Alphs (2014) 'Body mass index and metabolic parameters in patients with schizophrenia during long-term treatment with paliperidone palmitate', BMC Psychiatry, 14(1). doi: 10.1186/1471-244X-14-52.

Sugai, T., Yutaro Suzuki, Naoki Fukui, Junzo Watanabe, Shin Ono, Nobuto Tsuneyama, and Toshiyuki Someya (2012) 'Excessive insulin secretion in japanese schizophrenic patients treated with antipsychotics despite normal fasting glucose levels', Journal of Clinical Psychopharmacology, 32(6), pp. 750–755. doi: 10.1097/JCP.0b013e3182742ea4.

Teff, K. L, Michael R. Rickels, Joanna Grudziak, Carissa Fuller, Huong-Lan Nguyen, and Karl Rickels (2013) 'Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease', Diabetes, 62(9), pp. 3232–3240. doi: 10.2337/db13-0430.

Vancampfort, D. *et al.* (2016) 'Diabetes mellitus in people with schizophrenia , bipolar disorder and major depressive disorder : a systematic review and large scale

meta-analysis', (June), pp. 166–174.

Volpato, A. M. and Zugno, A. I. (2013) 'Recent evidence and potential mechanisms underlying weight gain and insulin resistance due to atypical antipsychotics', pp. 295–304. doi: 10.1590/1516-4446-2012-1052.

Wei, J., Earl Hsien-Jie Tan, Chia Eng Chong, Yiwei Ng, Ruki Wijesinghe, (2016) 'Physical side effects of Psychoactive meds Atypical antipsychotics : A review on the prevalence , monitoring , and management of their metabolic and cardiovascular side effects Changes in Body Weight'. doi: 10.9740/mhc.2016.07.178.

Whicher, C. A., Price, H. C. and Holt, R. I. G. (2018) 'Antipsychotic medication and type 2 diabetes and impaired glucose regulation', pp. 245–258.

Whiting, D. R. *et al.* (2011) 'IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030', Diabetes Research and Clinical Practice. Elsevier Ireland Ltd, 94(3), pp. 311–321. doi: 10.1016/j.diabres.2011.10.029.

Wu, X., Zeping huang, hongying han, Zhiyong Zhong, Zhaoyu gan, Xiaofeng guo, Feici Diao, Zili han, Jingping Zhao (2014) 'The comparison of glucose and lipid metabolism parameters in drug-naïve, antipsychotic-treated, and antipsychotic discontinuation patients with schizophrenia', Neuropsychiatric Disease and Treatment, 10, pp. 1361–1368. doi: 10.2147/NDT.S63140.

Xu, H. and Zhuang, X. (2019) 'Atypical antipsychotics-induced metabolic syndrome and nonalcoholic fatty liver disease: A critical review', Neuropsychiatric Disease and Treatment, 15, pp. 2087–2099. doi: 10.2147/NDT.S208061.

Yogaratnam, J., N Biswas, R Vadivel, R Jacob (2013) 'Metabolic Complications of Schizophrenia and Antipsychotic Medications — An Updated Review', pp. 21–28.

Zhang, Y. , Yingyu Liu†, Yingying Su, Yueyue You, Yue Ma, Guang Yang, Yan Song, Xinyu Liu, Mohan Wang, Lili Zhang and Changgui Kou (2017) 'The metabolic side effects of 12 antipsychotic drugs used for the treatment of schizophrenia on glucose: A network meta-analysis', BMC Psychiatry. BMC Psychiatry, 17(1), pp. 1–9. doi: 10.1186/s12888-017-1539-0.

APENDEX A: Information for participants

THE UNIVERSITY OF ZAMBIA

DIRECTORATE OF RESEARCH AND GRADUATE STUDIES

SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY

Self-introduction:

My name is Makame Pandu, I am a student at the University of Zambia pursuing a Master Degree of Medicine in Psychiatry in the School of Medicine, Department of psychiatry. The following is a short summary of this study to help you decide whether to be a part of this study.

Title of Research:

"Optimization of Early Diagnosis of Glucose Metabolism Impairment for Patients Receiving Antipsychotic Medications at Outpatient Psychiatric Clinic of the University Teaching Hospital in Lusaka".

Purpose of the Study:

You are being invited to take part in this research study that aim to Optimize the Early Diagnosis of Glucose metabolism impairment In Patients with Psychiatric disorders Receiving Antipsychotic Medication At Psychiatric Outpatient Clinic Of The University Teaching Hospital In Lusaka Zambia. This will help to determine the burden of the problem in this population group, and help medical professionals practicing in mental health services to improve their art of clinical practice in mental health care services particularly when they want to prescribe antipsychotics medications to their clients.

On the other hand, those patients who will be found to be having glucose metabolism impairment and at higher risk of developing diabetes type 2 will be given appropriate medical help and advice or will be referred to appropriate specialist for further evaluation and managements.

Why you have been chosen to participate?

I have identified you as one of the participants because you will be able to provide me with information needed for this research. You are attending an outpatient psychiatric clinic review here at University Teaching Hospital as such you are the right participant for this study as it is only being conducted in this Hospital. You will not be alone, I have identified other patients with psychiatric disorder attending their clinical review in this hospital who are willing to participate in this study.

Description of the Study and Your Involvement:

The objective of this study is to Optimize the Early Diagnosis of Glucose metabolism impairment In Patients with Psychiatric disorder Receiving Antipsychotic Medication At Psychiatric Outpatient Clinic Of The University Teaching Hospital In Lusaka Zambia.

Confidentiality:

All the information provided during the course of this exercise will be used ONLY for the purpose of this study. You DO NOT have to provide your name or any other personal details apart from what is needed in this study.

Voluntary Participation and Withdrawal: Your participation on this study is voluntary. You are free to participate or not. You are also free to withdraw at any point and should you feel uncomfortable to answer any question(s), you are free not to answer. However, your participation will be greatly appreciated and valued.

Risks of taking part in this study

Some of the procedure involved in this study may induce some discomfort though they are not harmful to your personal health.

Benefits of taking part in this study

Your participation in this study will have the following benefits:

By participating in this study, you are contributing to the general knowledge, focus and attention on glucose metabolism impairment in patients with psychiatric disorder receiving antipsychotic medications.

If the problem detected, you will be followed up and receive medical treatment at our hospital, The University Teaching Hospital (UTH).

Also the medical professionals practicing in mental health services will be aware with the burden of glucose metabolism impairment in population with psychiatric disorder and will utilize this knowledge in improving the services in their daily practices.

Compensation/Reimbursement

No compensation/reimbursement for participants as the study is purely for education purpose. However participation in this study can result extra visit to our clinic, where such happen you will be compensated for your time with a transport allowance of minimum of K30.00.

Who to contact?

In an event that you have any questions about this study or you feel unfairly treated by the researcher during the sessions, you can contact the following:

1. The study Supervisor

Dr. Anatolii Tsarkov

Mobile +26 (097) 4600980; +26 (095) 3662605

The University of Zambia

Ridgeway Campus

2. The Chairperson

UNZABREC

Tel: +260975338518/ 0968190319

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The University of Zambia

Ridgeway Campus.

3. Principal Investigator

Dr. Pandu Makame

Mobile +026076156070

Department of Psychiatry

The University of Zambia,

Ridgeway Campus.

APPENDIX B: INFORMED CONSENT FORM FOR PARTICIPANTS

THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY

P. O. Box 32379, Lusaka, Zambia

PLEASE READ THIS DOCUMENT CAREFULLY. SIGN YOUR NAME BELOW ONLY IF YOU AGREE THAT YOU WIIL PARTICIPATE AND YOU FULLY UNDERSTAND YOUR RIGHTS. YOUR SIGNATURE IS REQUIRED FOR YOUR PARTICIPATION.

Self-introduction:

My name is Makame Pandu, I am a student at The University of Zambia pursuing a Master Degree of Medicine in Psychiatry in the School of Medicine, Department of psychiatry. The following is a short summary of this study to help you decide whether to be a part of this study.

Description of the Study:

You are invited to take part in a study titled "OPTIMIZATION OF EARLY DIAGNOSIS OF GLUCOSE METABOLISM IMPAIRMENT FOR PATIENTS RECEIVING ANTIPSYCHOTIC MEDICATIONS AT UTH OUTPATIENT PSYCHIATRIC CLINIC''

You will be required to provide some information regarding your demographical data and you will undergo some test to check your glucose metabolic status as the aim of this study.

Time Involvement

The whole process will take approximately 30 minutes and not more than one hour.

Risks and Benefits:

1. You may experience some discomfort due to the procedure of the test and length of time required for the testing process.

2. We cannot guarantee that you will receive any direct benefits from this study though you will have an opportunity to know your glucose metabolism status, and contribute to knowledge that will help to know the actual situation and help in improvement of the mental health services in our practices.

Participation Rights:

1. Participation in this study is purely voluntary so that if you decide to withdraw at any point, the care or benefit you receive will not be affected by your withdrawal from the study.
2. All personal identifying information will be kept confidential and the data sheets will be kept in secured lockers in accordance with the standards of the University of Zambia Biomedical Research Ethics Committee (UNZABREC).

I……. (Name) have read and understood the terms and conditions of this study and I hereby agree to participate in the above-described research study. I understand that my participation is voluntary and that I may withdraw my participation at any time without penalty. My signature under here testifies that I understand the consent process and management of confidentiality as indicated above. I also understand that I can withdraw my participation at any time.

Signature of research participant: …….……Date…….....

Thumb print of research participant.....

Name of witness: …….....

Signature of witness.....Date.....

Name of researcher: …….....…….....

<u>Original form to:</u>

Research Team File

Copies to:

Participant

Medical Records (if applicable)

APPENDIX C: Participant's questionnaire

THE UNIVERSITY OF ZAMBIA

DIRECTORATE OF RESEARCH AND GRADUATE STUDIES

SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY

Date (recruitment day)……

Participant's demographic information

Number of interviewee…… Age …… …….

Address…….. Sex…….

Anthropometric measurements

Weight ……... Height …….

Body mass index (BMI) …… Waist circumference ……

Treatment information

Diagnosis……. Date of diagnosis…….

Medication on…….. Dosage ……..…….

Duration of treatments…….. Dosage of the drug……..

Adjuvant treatment if any……..

Blood glucose information

Random blood glucose (RBG)……

Fasting blood glucose (FBG)……

Other relevant information

Blood pressure

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

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IRB00001131 of IORG0000774

12th April 2021

Your REF. No. 1570-2021

Dr. Makame Haji Pandu,
University of Zambia,
Department of Psychiatry,
P.O Box 50110,
Lusaka.

Dear Dr. Pandu,

RE: OPTIMIZATION OF EARLY DIAGNOSIS OF GLUCOSE METABOLISM IMPAIRMENTS FOR PATIENTS WITH PSYCHOTIC DISORDER RECEIVING ANTIPSYCHOTIC MEDICATIONS ATTENDIND OUTPATIENT PSYCHIATRIC CLINIC AT UNIVERSITY TEACHING HOSPITAL IN LUSAKA -ZAMBIA (VERSION 1, 22.02.2021) (REF. NO. 1570-2021)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 12th April, 2021. The proposal is **approved**. The approval is based on the following documents that were submitted for review:

a) Study proposal
b) Questionnaires
c) Participant Consent Form

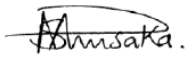
APPROVAL NUMBER : REF. 1570-2021

This number should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE : 12th April 2021**
- **TYPE OF APPROVAL : Standard**
- **EXPIRATION DATE OF APPROVAL : 11th April 2022**
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the UNZABREC Offices should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING**: All SAEs and any other serious challenges/problems having to do with participant welfare, participant safety and study integrity must be reported to UNZABREC within 3 working days using standard forms obtainable from UNZABREC.

- **MODIFICATIONS**: Prior UNZABREC approval using standard forms obtainable from the UNZABREC Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report must be submitted to the UNZABREC using standard forms obtainable from the UNZABREC Offices.
- **NHRA:** You are advised to obtain final study clearance and approval to conduct research in Zambia from the National Health Research Authority (NHRA) before commencing the research project.
- **QUESTIONS**: Please contact the UNZABREC on Telephone No.256067 or by e-mail on unzarec@unza.zm.
- **OTHER**: Please be reminded to send in copies of your research findings/results for our records. You're also required to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study. Use the online portal: unza.rhinno.net for further submissions.

Yours sincerely,



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NATIONAL HEALTH RESEARCH AUTHORITY

Paediatric Centre of Excellence, University Teaching Hospital, P.O. Box 30075, LUSAKA

Tell: +260211 250309 | Email: znhrasec@gmail.com | www.nhra.org.zm

Ref No:……. **Date: 9th July, 2021**

The Principal Investigator
Dr. Makame Haji Pandu,
University of Zambia,
Department of Psychiatry,
P.O Box 50110,
Lusaka, Zambia.

Dear Dr. Pandu,

Re: Request for Authority to Conduct Research

The National Health Research Ethics Board (NHREB) is in receipt of your request for authority to conduct research titled **"Optimization of Early Diagnosis of Glucose Metabolism Impairments for Patients with Psychotic Disorder Receiving Antipsychotic Medications attending Outpatient Psychiatric Clinic at University Teaching Hospital in Lusaka -Zambia."**

I wish to inform you that following submission of your request to the Board, its review of the same and in view of the ethical clearance, this study has been **approved** on condition that:

1. **A Material Transfer Agreement is obtained and cleared by the National Health Research Ethics Board should there be any need for samples to be sent outside the country for analysis.**
2. The relevant Provincial and District Medical Officers where the study is being conducted are fully appraised;
3. Progress updates are provided to NHRA quarterly from the date of commencement of the study;
4. The final study report is cleared by the NHRA before any publication or dissemination within or outside the country;
5. After clearance for publication or dissemination by the NHRA, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, and all key respondents.

Yours sincerely,

Prof. Patrick Musonda
Chairperson
National Health Research Ethics Board