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Prevalence of Impaired Glucose Regulation (IGR) among Schizophrenic Clients in Northern West-Bank

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Dedication

To my family

Acknowledgment

It is my pleasure to thank all the staff members of governmental psychiatric healthcare centers in North West Bank .

الإقرار

أنا الموقع أدناه مقدم الرسالة التي تحمل العنوان :

Prevalence of Impaired Glucose Regulation (IGR) among Schizophrenic Clients in Northern West-Bank

أقر بأن ما اشتملت عليه هذه الرسالة إنما هي نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككل، أو أي جزء منها لم يقدم لنيل أية درجة أو لقب علمي أو بحثي لدى أية مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name : **اسم الطالب :**

Signature : **التوقيع:**

Date: **التاريخ:**

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List of Abbreviations

Abbreviation	Full Name
ADA	American Diabetes Association.
BMI	Body Mass Index.
CATIE	Clinical Antipsychotic Trial of Intervention Effectiveness.
CI	Confidence Interval .
CPZeq	Chlorpromazine Dose Equivalences.
CUTLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study.
DM	Diabetes Mellitus.
DSM-IV	Diagnostic and Statistical Manual Mental Disorder.
FBG	Fasting Blood Glucose.
FFA	Free Fatty Acid.
FGA	First Generation Antipsychotic.
HbA1c	Glycosylated Hemoglobin.
HOMA-IR log	Homeostasis Model Assessment Insulin Resistance Logarithm.
HR	Hazard Ratio.
IFG	Impaired Fasting Glucose.
IGR	Impaired Glucose Regulation.
IGT	Impaired Glucose Tolerance.
IRB	Institutional Review Board .
MLR	Multiple Logistic Regression.
MOH	Ministry of Health.
NGO	Non Governmental Organization.
NIMH	National Institute of Mental Health
SD	Standard Deviation
SE	Standard Error
SGA	Second Generation Antipsychotic
T2DM	Type Π Diabetes Mellitus
TG/HDL	Triglycerides /High Density Lipoprotein
UNRWA	United Nations Relief and Works Agency
WC	Waist Circumstances
WHO	World Health Organization

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Abstract

Background and Objectives: To investigate the prevalence of pre-diabetes mellitus (Pre DM) and diabetes mellitus (DM) in clients with schizophrenia who use antipsychotic drugs and compare it with those published in the general population.

Methodology: A cross- sectional study carried out in 4 governmental primary psychiatric healthcare centers in northern West-Bank (Nablus, Jenin, Qalqilia, Tulkarm). Fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) were tested. Both the World Health Organization (WHO) and American Diabetes association (ADA) criteria for definition of pre-DM and DM were used in the study. Dysglycemia was defined as FBG> 110 mg/dl.

Result: The total number of samples is 250 clients . Based on WHO criteria, 27 clients (10.8%) were diabetic and 34 (13.6%) clients were pre-diabetic. The prevalence of pre-DM was significantly higher than that reported in the Palestinian general population. However, prevalence of DM was not significantly differently from that in the general population in Palestine. Regression analysis showed that advancing age and abnormal waist circumference were significant factors associated with dysglycemia in clients with schizophrenia.

Conclusion: This study confirmed the high prevalence of dysglycemia among patients diagnosed with schizophrenia, supporting the need for enhanced monitoring for diabetes in this population. It is likely that the presence of primary risk factors is more important in the development of dysglycemia in patients with schizophrenia than exposure to antipsychotic drug.

Chapter One
Introduction

1.1 Overview

In recent years, researchers have identified that people diagnosed with schizophrenia are at an increased risk of glucose dysregulation and that this risk is more common among patients treated with SGA **(Group 1988; Everson, Goldberg et al. 1998; Buse 2002; Knowler, Barrett-Connor et al. 2002; Perez-Iglesias, Mata et al. 2009)**. This metabolic adverse effect has significant implications in terms of both the cost of treatment and the disease burden for patients with mental illness.

Impaired glucose regulation or pre-diabetes represents a metabolic stage intermediate between normal glucose homeostasis and diabetes. Pre-diabetes is also referred to as borderline diabetes, impaired glucose tolerance (IGT), and/or impaired fasting glucose (IFG) **(Buysschaert and Bergman 2011)**. Pre-DM sometimes progresses to full picture of diabetes mellitus (DM) and is also reported to be a factor for increased mortality **(Barr, Zimmet et al. 2007; Nichols, Hillier et al. 2007)**. Studies about physical health in patients with mental illness are lacking in the Arab world in general and in Palestine in particular **(Jaalouk, Okasha et al. ; Okasha, Karam et al. 2012)**. In Palestine, there are 4 providers of primary healthcare: the Ministry of Health (MOH), which is the main health provider and responsible for supervision, regulation, licensure and control

of the whole health services. Other health providers include UNRWA, health services belonging to national and international non-governmental organizations (NGOs) and some private health sector (for profit) organizations. In the West Bank, where the study took place, mental health care services are provided by the government, and by few non-governmental organizations. Several governmental psychiatric primary health care centers are located throughout West-Bank. However, most of these centers are under-staffed and under-resourced **(Afana, Dalgard et al. 2002)**.

An important aspect of physical-health of patients with mental illness that requires monitoring and screening is glucose metabolic disorders. Studies about glucose metabolic disorders among patients with schizophrenia are important to help identify physical health problems in this neglected category of patients and improve their survival. Monitoring of glucose disturbances and other metabolic disorder might be a key element in enhancing the physical health in patient with schizophrenia who have shorter life span than non-schizophrenic patients **(Copeland, Zeber et al. 2009; Dervaux and Laqueille 2009; Sperling and Biermann 2009; Tiihonen, Lonnqvist et al. 2009)**. Therefore, this study was carried out to assess the prevalence of pre-DM and DM among sample of schizophrenic patients in Palestine.

1.2 Schizophrenia and Antipsychotic Medications

Schizophrenia is a severe mental disorder that affects approximately one percent(1%) of the various populations throughout the world **(Van Os, Hanssen et al. 2001; Crismon ML 2002; Van Os and Kapur 2009)**. The symptoms commonly seen in this mental disorder can be grouped into three major categories: positive symptoms (e.g. hallucinations and delusions), severe negative symptoms (e.g. flattened affect, lack of motivation, and impoverished speech or behavior), and cognitive deficits (e.g. impaired executive functioning, impaired working memory, decreased attention) **(Andreasen and Olsen 1982; Liddle 1987; Malla, Norman et al. 1993; Van Os, Hanssen et al. 2001; Van Os and Kapur 2009)**.

Antipsychotic drugs are the mainstay therapy for schizophrenia. The first antipsychotic drug, chlorpromazine, was approved for use in psychiatry in the early 1950's **(Meyer and Simpson 1997)**. Chlorpromazine revolutionized care for the mentally ill patients and provided a new way of treatment in addition to invasive procedures such as electroconvulsive shock therapy and insulin shock therapy. Today, there are two generations of antipsychotic agents on the market primarily used for treatment of schizophrenia: First Generation Antipsychotics (FGA) and Second Generation Antipsychotics (SGA).

1.2.1 First Generation Antipsychotics (FGA)

First-generation antipsychotic agents, also known as typical agents, include: chlorpromazine; fluphenazine; haloperidol; perphenzaine;and thioridazine (Table 1.1). These drugs are classified together because of the similar therapeutic effects that they have on positive symptoms as well the mechanism by which they work. These agents are further classified into low, medium, and high-potency agents. High-potency agents include haloperidol and fluphenazine, and have a daily dose of a few milligrams, whereas low-potency agents include chlorpromazine and thioridazine which have higher daily doses **(Joseph. Dipiro, Robert L. Talbert et al. 2011)**. First generation antipsychotic agents act by inhibiting dopamine (D2) receptors. Specifically, these drugs block post-synaptic dopamine receptors in the brain, in areas such as the frontal cortical region and limbic region **(Tadori, Forbes et al. 2009)**. The efficacy of the FGA in the acute management of schizophrenia is well established **(Hirsch s and Barnes T 1995)**. These agents have been demonstrated to reduce the intensity of positive symptoms, shorten acute episodes or exacerbations, and reduce the likelihood of recurrence **(Hirsch s and Barnes T 1995)**. These agents appear to have little effect on affect, cognitive symptoms or negative symptoms **(Kapur and Remington 2001)**.

Adverse effects of FGA include: antihistaminic (sedation); antidopaminergic D2 (extrapyramidal side-effects and hyperprolactinemia); anticholinergic (dry mouth, blurred vision, constipation, urinary retention,

sinus tachycardia, cognition and memory effects; and anti- α1- adrenergic effects (reflex tachycardia and orthostatic hypotension) **(Nakayama, Yakutsu et al. 1999)** (Table 1.3). Typically, the lower potency agents cause more sedation and hypotension, and the high potency agents more extrapyramidal side effects **(Crismon ML 2002)**. It is the extrapyramidal effects, particularly tardive dyskinesia, that limit the usefulness of these agents. Among the FGA, the low-potency agents, in particular chlorpromazine have been associated with glucose intolerance **(Haddad 2004)**. Side effects of FGA may eventually lead to non-compliance with medication, especially when severe side-effects such as drug-induced Parkinsonism and tardive dyskinesia are present **(Linden, Scheel et al. 2006)**.

1.2.2 Second Generation Antipsychotics (SGA)

Clozapine, the first agent in this class, was licensed in the United States of America in 1989 **(Clozaril. 2004)**. Other SGA include: aripiprazole; olanzapine; quetiapine; risperidone; and ziprasidone (Table 1.2) . In contrast to FGA, the SGA act on multiple receptors sub-types with a range of affinity for dopamine, serotonin, and histamine, muscarinic and adrenergic receptors **(Markowitz, Brown et al. 1999; Bymaster, Felder et al. 2003; Kroeze, Hufeisen et al. 2003; Nasrallah 2008)**. The second-generation agents inhibit dopamine D2 receptors, but to a lesser extent than the FGA. The second-generation agents exhibit a high affinity for serotonin 5-HT2A receptors **(Seeman 2002; Tort, Souza et al. 2006)**. The SGA are

more effective than placebo in treating both the positive and negative symptoms of schizophrenia, **(Leucht, Pitschel-Walz et al. 1999; Davis and Chen 2003)**. When compared to the first generation antipsychotics, these agents have been found to have comparable efficacy in treating the positive symptoms, and superior efficacy in treating both the negative symptoms and cognitive deficits of schizophrenia **(Leucht, Pitschel-Walz et al. 1999; Davis and Chen 2003; Davis, Chen et al. 2003)**. SGA drugs have generally been found to be at least as effective as, or more effective than FGA drugs in terms of reducing both positive and negative symptoms **(Hafner, Hambrecht et al. 1998)**. Recent evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) did not find SGA drugs quetiapine or risperidone superior to the typical antipsychotic drug perphenazine, in terms of time to discontinuation **(Lieberman, Stroup et al. 2005)**. Furthermore, the British Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS) found that patients randomly switched to an SGA drug other than clozapine compared to patients randomly switched to a FGA drug did not experience any benefits in terms of quality of life, positive and negative symptoms or associated costs following 1 year of treatment **(Jones, Barnes et al. 2006)**. Risperidone has been shown to be at least as effective as FGA drugs in reducing schizophrenia symptoms and superior to some specific FGA agents such as haloperidol **(Csernansky, Mahmoud et al. 2002)**. Risperidone has a longer time to all cause discontinuation and lower re-hospitalization rates compared to haloperidol **(Csernansky, Mahmoud et**

al. 2002). Olanzapine has been shown to be at least as effective as FGA in symptom reduction and some controlled trials have also found olanzapine to be superior to haloperidol in decreasing total psychopathology and negative symptoms **(Meltzer and Fibiger 1996)**. Meta analyses have found quetiapine to be of similar efficacy to haloperidol **(Davis and Chen 2003)**. In clinical practice, the SGA have been deemed more effective than the FGA due to a lower propensity to be prematurely discontinued **(Jaffe and Levine 2003).**

The relative effectiveness amongst the SGA drugs has been examined, particularly in the CATIE trial **(McEvoy, Lieberman et al. 2006)**. Phase II of the CATIE trial found time to treatment discontinuation as follows: risperidone (median: 7 months), olanzapine (6.3 months), quetiapine (4.0 months) and ziprasidone (2.8 months). A greater time to treatment discontinuation is desirable; if a patient discontinues drug treatment, then this can indicate the drug does not provide adequate symptom relief or the drug may cause undesirable side effects. Phase I of the CATIE trial found olanzapine superior to both quetiapine and risperidone in terms of time to discontinuation. Reasons for discontinuation differed between the drugs with olanzapine mostly discontinued due to adverse events such as weight gain and metabolic effects while quetiapine and risperidone were often discontinued due to lack of efficacy **(Crismon ML 2002)**. In patients with schizophrenia, clozapine has been found to be superior to other atypical drugs in terms of symptom reduction, time to

discontinuation, reduction of suicide attempts, and costs of re-hospitalizations **(Geodon 2004; Seroquel 2004; zyprexa 2004)**

As with the FGA, the SGA can cause a wide range of adverse effects including: antihistaminic; antidopaminergic; anticholinergic; and anti-α1-adrenergic effects. (Table 1.3)Comparatively, however, the SGA are more tolerable **(Wirshing 2001; Dubisar, Stoner et al. 2004)**. In particular, the SGA, with the exception of risperidone, have a reduced propensity to cause extrapyramidal side effects **(Davis and Chen 2002)**. Agranulocytosis, , myocarditis and an increased propensity to lower the seizure threshold, are serious side effects associated with clozapine and limit its use to that of second-line therapy **(Clozaril. 2004)**. Clozapine is recommended for use in patients who have failed to respond to another antipsychotic drug **(Glick, Murray et al. 2001)**. There is growing concern about the risks of weight gain, metabolic problems and diabetes induced by SGA agents **(Geddes, Freemantle et al. 2000)**. A number of case reports, chart studies and large scale studies have provided evidence of antipsychotic induced diabetes. However, not all drugs appear equal in terms of their risks to induce DM **(Mason 1980; Haupt and Newcomer 2001; Newcomer, Haupt et al. 2002; Leucht, Wahlbeck et al. 2003; Jin, Meyer et al. 2004)**.

1.3 Mechanisms of Antipsychotic- Induced Glucose Dysregulation

In a healthy individual, glucose is absorbed from GIT and is then utilized by cells to produce energy or convert excess glucose into fat for storage. Glucose level in blood is regulated by the hormone insulin **(Nair 2007)**. Diabetes occurs when the body cannot properly regulate blood glucose level due to insulin resistance or when there is an insufficient amount of insulin. Insulin resistance or insufficient insulin results in the inability of glucose to move into the cells which leads to glucose accumulation in the blood, eventually causing hyperglycemia. Acute hyperglycemia can lead to life threatening complications such as ketoacidosis.

. Studies in some developing countries indicated that the prevalence of DM is estimated to be 4.5 % in the general population and 16%- 25% in patients with schizophrenia **(Mukherjee, Decina et al. 1996; Dixon, Weiden et al. 2000)**. One mechanism of antipsychotic-induced diabetes is through direct effects of antipsychotic drugs on insulin resistance. Antipsychotic drugs may have a direct effect on insulin-sensitive target tissues leading to impairment of glucose transporter function even in the absence of weight gain **(Henderson 2002)**. Another mechanism of antipsychotic-induced diabetes is via weight gain, which can lead to insulin resistance and hyperglycemia **(Melkersson and Dahl 2004; Saddichha, Manjunatha et al. 2008; Parsons, Allison et al. 2009)**. SGA drugs such

as olanzapine and clozapine are associated with the greatest amount of weight gain **(Baptista, Kin et al. 2004)**. Significant weight gain has also been observed with FGA drugs, especially with chlorpromazine and thioridazine **(Baptista, Kin et al. 2004)**. The primary effect of antipsychotic medication on weight gain is through appetite stimulation and increased food intake in the absence of compensatory increase in energy expenditure **(Hafner and an der Heiden 1997)**. An increase in prolactin levels, caused mainly by FGA drugs may also lead to weight gain **(McIntyre, Mancini et al. 2001)**. SGA may possibly enhance a brain chemical function which may cause weight gain **(McIntyre, Mancini et al. 2001)**. Significant increases in hunger, food intake, decreased satiety and binge eating behavior are potential mechanisms for weight induced side effects of antipsychotic medications **(Case, Treuer et al. ; Fountaine, Taylor et al. ; Roerig, Mitchell et al. 2005; Kluge, Schuld et al. 2007; Blouin, Tremblay et al. 2008)**. Consistent with the findings on weight gain, epidemiological studies consistently demonstrate that the two SGAs with the metabolic profiles most predictive of DM are olanzapine and clozapine **(Ashim, Warrington et al. 2004; Cohen 2004; Melkersson and Dahl 2004; Nasrallah and Newcomer 2004)**, while ziprasidone has been shown to improve metabolic parameters. A recent meta-analysis reviewed data from 48 randomized blinded studies comparing the SGAs and found that olanzapine produced greater weight gain and higher glucose and cholesterol levels than any of the other drugs including clozapine **(Rummel-Kluge, Komossa et al. 2010).** Cross-sectional clinical studies

also provide evidence of abnormal glucose metabolism and insulin resistance in schizophrenic patients on olanzapine and clozapine **(Haupt and Newcomer 2002; L'Italien, Casey et al. 2007; Scheen and De Hert 2007; van Winkel, De Hert et al. 2008)**. Olanzapine has been shown to induce higher levels of glucose and insulin at baseline **(Lindenmayer, Czobor et al. 2003; Wu, Zhao et al. 2006)** and during oral glucose tolerance **tests (Lindenmayer, Czobor et al. 2003; Saddichha, Manjunatha et al. 2008)** although a study reported no effects **(Newcomer 2004)**.

Mokdad (2003) has found that severely overweight men had an OR of 7.4 for diabetes compared to age-matched men with a healthy weight **(Mokdad, Ford et al. 2003)**. Age is another major risk factor for diabetes; rates of diabetes are much higher in older populations (Pan, Yang et al. 1997). Family history of diabetes and ethnicity are also risk factors for the development of DM **(Hafner and an der Heiden 1997)**. Additionally, a diagnosis of schizophrenia may increase the risk for diabetes. Untreated patients with schizophrenia have been shown to have more glucose abnormalities including insulin resistance compared to healthy controls **(Ryan, Collins et al. 2003)**.

Metabolic dysregulation manifesting initially as weight gain can rapidly result in obesity, with concurrent dyslipidemia and impaired glucose tolerance which may develop into DM. A further consequence of these adverse effects can be cardiovascular disease that is likely to

contribute to the reduced life expectancy and increased incidence of cardiovascular death among people with severe mental illness **(Osborn, Levy et al. 2007)**. Thus antipsychotic drug induced metabolic disturbance is one of the greatest concerns of current psychiatric pharmacotherapy, and is most usefully assessed by the presence of metabolic syndrome. Metabolic syndrome identifies a group of obesity-related risk factors for chronic metabolic and cardiovascular disease **(Alberti, Zimmet et al. 2005)**. It is a useful concept with a strong predictive value for consequent diabetes and cardiovascular disease in the general population and it is now increasingly considered as a useful indicator of metabolic risk in psychiatry. An international consensus definition concentrates on the core symptom of central obesity, easily measured by waist circumference and reflecting the deep visceral intra-abdominal fat, in addition to further cardiovascular (blood pressure, lipids) and diabetic (fasting glucose) measures indicating metabolic pathology **(Alberti, Zimmet et al. 2005)**. Metabolic syndrome represents a group of risk factors for type II diabetes. Metabolic syndrome is diagnosed when 3 or more of the following are present: increased weight around the waist, high levels of triglycerides, low levels of high-density lipoproteins cholesterol, high blood pressure, and high fasting blood glucose levels **(Lorenzo, Okoloise et al. 2003)**.

In addition to the reported effects on glucose metabolism, olanzapine and clozapine have been associated with increased fasting triglyceride (TG) concentrations **(Meyer 2002; Koro and Meyer 2005; Chiu, Chen et al.**

2006) and low density lipoproteins. The effects of olanzapine on plasma free fatty acid (FFAs) levels are inconsistent. One study reported an increase in FFA levels in patients on chronic treatment with antipsychotic agents **(Screening ; Wang, Zhang et al. 2006)** but when olanzapine was administered to healthy subjects, a decrease in fasting free fatty acid levels and a blunted suppression of free fatty acid levels during a euglycemic, hyperinsulinemic clamp **(Vidarsdottir, de Leeuw van Weenen et al. 2009)** Were observed.

1.4 Objectives of the Study

1. To investigate the fasting blood glucose (FBG) and prevalence of pre-diabetes (pre-DM) and DM among clients with schizophrenia.

2. To compare the prevalence of pre-DM and DM among clients with schizophrenia with those in the general population in Palestine.

3. To investigate significant factors associated with dysglycemia (FBG> 110 mg/ dL) among clients with schizophrenia.

1.5 Significance of the Study

1. For patients with schizophrenia, the intent of prescribed antipsychotic medications is to minimize symptoms and improve their quality of life. However, there are always risks associated with medications that must be weighed against the benefits they deliver. Identifying the nature and

prevalence of such risks will help physicians implement precautions to prevent or minimize the modifiable factors for such risks and develop treatment plans that address all aspects of patients' health. It is true that our study is a cross sectional one which might have less scientific rigor and rigidity than prospective studies, but is more easy to carry out.

2. A review of the literature failed to show studies carried out in Palestine or even in the Arab world regarding prevalence of metabolic disorders and its associate among patients with mental illness. Actually studies and published research in the field of mental health is few in the Arab world **(Jaalouk, Okasha et al. 2012)**. Therefore, our study will be one of the few in the Arab world in the field of health among patients with mental illness.

1.6 Research Questions and Hypotheses

This study was designed to examine four research questions

1. What is the mean FBG and prevalence of pre-DM and DM among clients with schizophrenia?

2. Is the prevalence of pre-DM in clients with schizophrenia higher than that reported in the general Palestinian population?

3. Is the prevalence of DM in clients with schizophrenia higher than that reported in the general Palestinian population?

4. Is there any association between prevalence of pre-DM/ DM in clients with schizophrenia and any tested variables?

The Hypotheses for the above research questions were as follows in the same order as research questions:

1. FBG among clients with schizophrenia is not significantly different from that of general population.

2. There is no difference in the prevalence of pre-DM among schizophrenic clients and those reported in the general population.

3. There is no difference in the prevalence of DM among schizophrenic clients and those reported in the general population.

4. There is no association between various demographic, clinical and medication variables and presence of dysglycemia (FBG≥110 mg/ dL).

Table 1-1: selected examples of first generation antipsychotic

Drug	Usual daily maintenance dosage	Dopamine D2 Neuroreceptor potency
Chlorpromazine	400 mg	Low
Thioridazine	200 to 300 mg	Low
Perphenazine	24mg	Medium
Fluphenazine	10 to 20 mg	High
Haloperidol	10 to 15 mg	High
Thiothixene	30 mg	High
Trifluoperazine	20 mg	High

Table 1- 2 selected examples of second generation antipsychotics

Drug	Year introduced	Usual daily dosage
Aripiprazole	2002	10 to 30 mg
Clozapine	1989	300 to 600 mg
Olanzapine	1996	10 to 20 mg
Quetiapine	1998	250 to 600 mg
Risperidone	1994	3 to 6 mg
Ziprasidone	2001	40 to 80 mg

Table 1-3 Comparative risk of adverse effects of antipsychotic medications

			SGAs					
Adverse effect	**Low potency FGAs**	**High Potency FGAs**	**Aripiprazole**	**Clozapine**	**Olanzapine**	**Quetiapine**	**Risperidone**	**Ziprasidone**
Anticholinergic effects	+++	+	**0**	+++	+	+	**0**	**0**
Dyslipidemia	++	+	**0**	+++	+++	++	+	**0**
Extrapyramidal symptoms	+	+++	+	**0**	+	**0**	++	+
Hyperprolactinemia	++	+++	**0**	**0**	+	**0**	+++	+
Neuroleptic malignant syndrome	+	++	+	+	+	+	+	+
Postural hypotension	+++	+	+	+++	+	++	++	+
Prolonged QT interval	++	+	+	+	+	+	+	++
Sedation	+++	+	+	+++	++	++	+	+
Seizures	+	+	+	+++	+	+	+	+
Sexual dysfunction	+++	++	+	+	+	+	++	+
Type 2 diabetes mellitus	+	+	+	++	++	+	+	+
Weight gain	++	+	**0**	+++	+++	++	++	**0**

NOTE : 0 = rare ; + = lower risk ; ++ = medium risk ; +++ = higher risk . FGAs = first generation antipsychotic; SGAs = second generation antipsychotic **(Gardner, Baldessarini et al. 2005)**.

Chapter 2
Literature Review

2. 1 Risk of development of DM by antipsychotic agents.

Pubmed search yielded several studies about risks of developing DM by antipsychotic agents. A large multi-site epidemiologic study found that the risk of diabetes for persons exposed to olanzapine, risperidone, and quetiapine was dose-dependent and elevated at therapeutic doses **(Ulcickas Yood, Delorenze et al. 2011)**. A study sought to determine which risk factors are of particular screening importance in monitoring the metabolic status of schizophrenic patients found that traditional risk factors such as obesity , family history of DM ,dislipidemia, hypertension, associated with DM are the factors most strongly associated with increased risk of diabetes in patients with schizophrenia **(Argo, Carnahan et al. 2011)**. Another study carried out to quantify the risk of DM associated with atypical antipsychotics compared with conventional antipsychotics found that compared with patients receiving FGA, the risk of diabetes was greatest among patients taking risperidone HR 3.8, 95% CI 2.7-5.3), olanzapine (3.7, 95% CI 2.5-5.3), and quetiapine (2.5, 95% CI 1.4-4.3) **(Gu, Reynolds et al. 2003)**. Different results were obtained by other researchers. A study found that relative to typical antipsychotics, aripiprazole, ziprasidone, risperidone and quetiapine were not associated with an increased risk of diabetes while olanzapine and clozapine were associated with an increased risk **(Yood, DeLorenze et al. 2009)**. A study

carried out to investigate 3-month changes in glucose metabolism in a naturalistic sample of patients with schizophrenia newly started on or switched to specific atypical antipsychotic medication therapy **(Van Winkel, De Hert et al. 2006; van Winkel, De Hert et al. 2008)**. The incidence of new-onset glucose abnormalities, including diabetes, in the first 3 months after newly starting or switching atypical antipsychotic medication is high and may be markedly influenced by type of prescribed antipsychotic **(Van Winkel, De Hert et al. 2006; van Winkel, De Hert et al. 2008)**. The authors emphasized the importance of accurately screening for new-onset glucose abnormalities after initiation of an atypical antipsychotic is emphasized. A study in Taiwan carried out to detect the incidence of diabetes in patients with schizophrenia found that increased age, females, hypertension, and hyperlipidemia were risk factors of diabetes in patients with schizophrenia **(Hsu, Chien et al. 2011)**. A study carried out to investigate and characterize the incidence of diabetes for people treated with antipsychotic medication in clinical practice found that treatment with FGA and SGAis associated with an increased risk of developing diabetes with large differences between individual drugs and that the risk increases with the duration of treatment and with polypharmacy of antipsychotic drugs **(Kessing, Thomsen et al. 2010)**. A retrospective study found that clozapine and olanzapine both posed a significantly increased risk of diabetes compared to use of a FGA; clozapine (HR=1.57 (95 % CI=1.31 -1.89), olanzapine (HR= 1.15 (CI=1.07 - 1.24) and that neither quetiapine nor risperidone posed a significant risk

for diabetes compared to a typical agent **(Leslie and Rosenheck 2004)**. A matched case control study found that clozapine and olanzapine but not quetiapine or risepridone pose a significantly increased risk of diabetes compared to use of typical antipsychotic drugs: clozapine (OR=1.36 (CI=1.16 1.55), olanzapine (OR=1.34 (CI=1.20 - 1.53) and that risks for olanazpine increased with dosage **(Lambert, Chou et al. 2005).** In a retrospective cohort study; clozapine, olanzapine and quetiapine pose significant risks for diabetes compared to FGA: clozapine (OR=1.25 (CI=1.07 - 1.46), olanzapine (OR=1.11 (CI=1.04 - 1.18), quetiapine (OR=1.31 (CI=1.11 - 1.55) while risperidone did not pose a significant risk of diabetes **(Sernyak, Leslie et al. 2002)**. A nested case control found that the use of olanzapine posed a significant risk for diabetes compared to use of typical antipsychotic drugs (OR=5.8 (CI=1.5 -10.9)) while risperidone did not pose a significant risk of diabetes. Clozapine and quetiapine were not included due to small sample size. **(Kornegay, Vasilakis-Scaramozza et al. 2002)**. A retrospective cohort study found that the use of olanzapine, risperidone or quetiapine did not significantly increase the risk of diabetes compared to use of FGA. Clozapine was not included in the study **(Barner, Worchel et al. 2004)**. A Case-control study found that use of clozapine and quetiapine significantly increased the risk of diabetes compared to use of FGA; clozapine (OR=2.06 (CI=1.07 - 3.99), quetiapine (OR=3.09 (CI=1.59 - 6.03)). Use of olanzapine or risperidone did not significantly increase the risk of diabetes compared to use of a typical antipsychotic **(Citrome, Jaffe et al. 2004)** . A Retrospective cohort study found that the

use of any antipsychotic drug significantly increased the risk of diabetes compared to a general patient population: low potency typical (HR=4.2 (CI=3.2 -5.5), risperidone (HR=3.4 (CI=3.1 - 3.8), clozapine (HR=3.3 (CI=1.4 -8.0), other typical (HR=3.1 (CI=2.6 - 3.7), olanzapine (HR=3.0 (CI=2.6 - 3.5), quetiapine (HR=1.7 (CI=1.2 - 2.4). Use of risperidone and not any other atypical antipsychotic increased the risk of diabetes compared to haloperidol users. A positive-dose response relationship was observed with low-potency drugs alone **(Buse, Cavazzoni et al. 2003)**. A retrospective cohort study found that the use of risperidone, olanzapine or thiordazine, a low-potency typical significantly increased the risk of diabetes compared to no use of an antipsychotic drug; risperidone (HR=2.5 (CI=1.4-4.5), olanzapine (HR=3.9 (CI=1.9-8.1), thiordazine (HR=1.7 (CI=1.1-2.5). Clozapine and quetiapine were not included in the study **(Carlson, Hornbuckle et al. 2006)**. A retrospective cohort study found that the use of clozapine, olanzapine, high potency FGA and low potency FGA significantly increased the risk of diabetes compared to no use of an antipsychotic: clozapine (OR=7.4 (CI=0.6 - 34.8), olanzapine (OR=3.1 (1.6 - 5.9), high potency FGA(OR=2.1 (1.1 - 4.1), low potency typicals (OR=3.5 (CI=1.5 -7.8). Use of risperidone did not increase the risk of diabetes compared to the general population **(Gianfrancesco, Grogg et al. 2002)**. A case-control study; found that the use of clozapine, olanzapine, risperidone or quetiapine significantly increased the risk of diabetes compared to use of FGA: clozapine (HR=7.0 (CI=1.7 - 28.9), olanzapine (HR=3.2 (2.7, 3.8), risperidone (HR=3.4 (2.8 - 4.2), quetiapine (HR=1.8

(1.4 - 2.4) **(Guo, Keck et al. 2007)**. A retrospective cohort design; found that the use of clozapine, olanzapine, risperidone or quetiapine did not significantly increase the risk of diabetes compared to use of FGA **(Ostbye, Curtis et al. 2005).**

Overall, clozapine and olanzapine appear to increase the risk of diabetes compared to use of FGA and no use of an antipsychotic drug. Furthermore, the few studies that have estimated the risk of diabetes in specific FGA have found low-potency FGA to pose an increased risk of diabetes compared to no use of an antipsychotic. The risks for risperidone, quetiapine and FGA (other than low-potency drugs) appear uncertain in terms of risks relative to other antipsychotic drugs.

2.2 Prevalence Studies of DM among schizophrenia patients.

A number of cohort studies have examined the prevalence of diabetes among patients taking antipsychotics **(Hagg, Joelsson et al. 1998; Henderson, Cagliero et al. 2000; Sernyak, Leslie et al. 2002; Gupta, Steinmeyer et al. 2003; Lamberti, Crilly et al. 2004; Lambert, Chou et al. 2005; Mackin, Watkinson et al. 2005; Cohen, Dekker et al. 2006)**. The prevalence of DM and IGTin these studies ranged from 9 to 36.6 percent, and in each instance was significantly greater than that noted in a similar age-matched general population. Association between the prevalence of glucose dysregulation and FGA or SGA varied. In a prospective study, Hagg et al (1998). assessed the prevalence of DMor IGT in patients treated with clozapine (N=63) compared to patients treated

with depot preparations of first-generation antipsychotics (N=67) **(Hagg, Joelsson et al. 1998)**. DM or IGT was documented in 22 percent of clozapine patients compared to 10 percent of the depot group, although the difference was not statistically significant (p=0.06) **(Hagg, Joelsson et al. 1998)**. Henderson et al. (2000) published a five-year naturalistic study in which 30 new cases of diabetes were diagnosed among 82 non-diabetic patients (36.6%) treated with clozapine In a similar study, Gupta et al. (2003) noted a prevalence of diabetes of 17 percent in a cohort of 208 patients (mean age 46 years (SD 14.5)) with serious mental illness receiving monotherapy with either FGA or SGA . No difference in the prevalence of diabetes was found between the different antipsychotic agents **(Gupta, Steinmeyer et al. 2003)**. Using data from the Veterans Health Administration of the Department of Veterans Affairs (VA), Sernyak et al. (2002) conducted a retrospective review comparing the prevalence of diabetes in 38,632 outpatients with schizophrenia receiving treatment with first- and second-generation antipsychotics. The prevalence of diabetes did not differ between patients receiving treatment with FGA and SGAwith rates of 18.64 percent and 18.84 percent, respectively **(Sernyak, Leslie et al. 2002)**. After controlling for the effect of age, patients receiving SGA were noted to be significantly more likely to have diabetes (odds ratio (OR): 1.09; 95% CI: 1.03-1.15, p=0.002) compared to those receiving a FGA**(Sernyak, Leslie et al. 2002)**. Stratifying by age, the effect was most pronounced for those aged less than 40 years (OR: 1.63; 95% CI: 1.23-2.16, p=0.001) with prevalence rates of 6.2 to 8.7

percent noted **(Sernyak, Leslie et al. 2002)**. In contrast to the study by Gupta et al. (2003) a significant difference in the prevalence of diabetes was found between the different antipsychotic agents **(Henderson, Cagliero et al. 2000; Gupta, Steinmeyer et al. 2003)**. Specifically, there was a significant association between the use of clozapine, olanzapine and quetiapine, but not risperidone, and a diagnosis of diabetes **(Sernyak, Leslie et al. 2002)**. Clearly prevalence data cannot be used to determine the incidence of diabetes associated with the use of SGA. These data merely serve to highlight the high prevalence of diabetes among patients with serious mental illness prescribed antipsychotic agents. This may relate to the use of antipsychotics, to a more diabetogenic lifestyle, or a genetic predisposition of this vulnerable population to the development of diabetes.

2.3 Prospective Trials for development of DM by antipsychotics

Prospective double-blind, randomized controlled-trials are the best-evidence for a cause and effect relationship. The most notable trial in this area is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a randomized active-control trial sponsored by the National Institute of Mental Health (NIMH), published in September 2005. The outcomes from this trial and other related trials will be discussed now.

2.3.1 The CATIE Study

The CATIE study was a double blind, active control clinical trial designed to compare the effectiveness and treatment-related adverse effects of the FGA and SGA agents **(Lieberman, Stroup et al. 2005)**. The trial included patients with a diagnosis of schizophrenia aged between 18 and 65. A total of 1,493 patients were randomized to receive olanzapine (N=330), quetiapine (N=329), risperidone (N=333), ziprasidone (N=183), or the FGA, perphenazine (N=257) for up to the 18 months **(Lieberman, Stroup et al. 2005)**. The majority of patients were male (74%), white (60%), with a mean age of 40.6 years (SD: 11.1). Prevalent diagnoses at baseline included: diabetes (11%); hyperlipidemia (14%) and hypertension (20%). The mean modal treatment doses were as follows: olanzapine 20.1 milligrams; quetiapine 543.4 milligrams; risperidone 3.9 milligrams; ziprasidone 112.8 milligrams; and perphenazine 20.8 milligrams. Consistent with trends in schizophrenia management, treatment was frequently discontinued with only 26 percent of patients continuing treatment for the planned 18 months. Similarly the time to treatment discontinuation was longest for olanzapine (median: 9.2 months), compared to quetiapine (4.6 months), risperidone (4.8 months), ziprasidone (3.5 months) and perphenazine (5.6 months). Of note, the agents differed in their rate of discontinuation because of treatment intolerance ($p=0.04$) even after adjusting for duration of exposure. Olanzapine was the most likely (18%), and risperidone the least likely (10%) to be discontinued owing to

intolerability **(Lieberman, Stroup et al. 2005)**. The agents differed significantly regarding treatment-related weight gain and changes in measures of glucose and lipid metabolism. Regardless of treatment duration, olanzapine was associated with the greatest increase in weight ($p<0.001$), glycosylated hemoglobin (HbA1C) ($p<0.001$), cholesterol ($p<0.001$) and triglycerides ($p<0.001$) from baseline and was significantly more likely to be discontinued because of these effects ($p<0.001$) than the other agents. The magnitude of the changes in these parameters is noteworthy. Exposure adjusted increases in mean blood glucose ranged from 2.9 mg/dL (standard error (3.4) for ziprasidone to 13.7mg/dL (SE: 2.5) for olanzapine ($p=0.59$). Exposure-adjusted changes in glycated hemoglobin (HbA1c) from baseline ranged from 0.04 percent (SE: 0.08) for risperidone to 0.40 percent (SE: 0.07) for olanzapine ($p=0.01$) **(Lieberman, Stroup et al. 2005)**. Changes of this scale are only likely to be problematic in a patient with a high baseline risk of diabetes, wherein a relatively small change in blood glucose could shift the patient from pre-diabetes (FBG : ≥100mg/dL) to diabetes (FBG ≥126mg/dL).

2.3.2 Glucose Control and Insulin Resistance

In a placebo-controlled, open-label study examining olanzapine-induced glucose dysregulation, patients treated with olanzapine experienced significant increases in fasting insulin concentrations and a rapid and significant increase in insulin-resistance **(Ebenbichler, Laimer et al. 2003)**. This was not associated with a change in beta cell function;

thereby opposing the hypothesis that olanzapine acts as a direct toxin on beta cells and suggesting instead that the mechanism of glucose dysregulation is due to an induction of peripheral insulin resistance. Compared to controls, patients treated with olanzapine (medication period 8.1 weeks) experienced significant increases in fasting plasma glucose levels (0.7mmol/L versus 0 mmol/L; p=0.009), weight (3.3Kg versus 0.6Kg; p=0.005) and, fasting insulin concentrations (4.5μU/mL versus -1.0 μU/mL; p=0.008) from baseline. While the association between weight gain and insulin resistance is well documented, the authors noted that this is unlikely to be the sole factor contributing to the development of insulin resistance due to the absence of weight gain in some patients and the rapid onset of insulin resistance **(Ebenbichler, Laimer et al. 2003)**.

In a randomized, controlled, double-blind, six-week trial (N=269) comparing olanzapine and ziprasidone, differences in the metabolic profile of the two agents were noted. Compared to ziprasidone, olanzapine was associated with greater increases in weight ($p<0.001$), body mass index ($p<0.0005$), fasting serum insulin (p=0.051), C-peptide (p=0.07), and homeostasis model assessment insulin resistance logarithm (HOMA-IR[log]) (p=0.08) – a measure which takes into account both fasting insulin and fasting glucose measures. Neither agent was noted to significantly affect fasting serum glucose levels with a median increase from baseline of one milligram per deciliter noted for both agents **(Simpson, Glick et al. 2004)**. In contrast to the study by Simpson et al.

2004, Howes et al. (2004) documented significant glucose dysregulation in 11 of 20 schizophrenia patients treated with clozapine that was not associated with significant changes in insulin levels or insulin resistance levels Changes in glucose control were also independent of changes in BMI. The authors hypothesized that glucose dysregulation may be secondary to a direct effect of clozapine in reducing neuronal glucose uptake leading to compensatory increases in glucose levels rather than to clozapine induced peripheral insulin resistance **(Howes, Bhatnagar et al. 2004)** Moreover, these authors subsequently found that changes in glucose control do not appear to be related to changes in growth hormone, insulin-like growth factor-1 or insulin-like growth factor binding protein-1 (all important glucoregulatory factors). This supports a theory of a possible direct effect of antipsychotics on central glucose regulation **(Howes, Gaughran et al. 2004)**. Kingsbury et al. (2001) examined the short-term effects of ziprasidone on BMI and serum glucose levels in a six-week, open-label, multi-center study (N=37)**(Kingsbury, Fayek et al. 2001)**. No significant change in BMI or serum glucose level was documented. Similar findings were documented in a fourteen-week, prospective, randomized trial where clozapine, olanzapine and haloperidol, but not risperidone, were associated with significant increases in plasma glucose levels in 101 patients with schizophrenia or schizoaffective disorder **(Lindenmayer, Czobor et al. 2003).**

2.4 Summary

While there are some inconsistencies in the findings of the various prospective studies, there nonetheless appears to be a trend towards greater dysregulation of glucose and insulin homeostasis with clozapine and olanzapine than with quetiapine, risperidone and ziprasidone. Given the magnitude of the changes noted, treatment with these agents could precipitate DM FPG ≥ 126 mg/dL) in a patient with Pre-DM(100 mg/dL ≤ FPG < 126mg/dL) or cause a non DM (FPG < 100mg/dL) to be re-classified as having pre-diabetes.

There are several hypotheses as to how antipsychotics may induce glucose dysregulation. These include a direct toxic effect on pancreatic islet cell receptors, via inhibition of dopamine D2 receptors or by antagonism of serotonin 5-HT1A and 5-HT2A/C receptors **(Wirshing, Spellberg et al. 1998; Wirshing, Pierre et al. 2001; Wirshing, Boyd et al. 2002; Ebenbichler, Laimer et al. 2003; Wirshing, Pierre et al. 2003)**. Alternatively, insulin resistance may arise due to treatment-induced weight gain and increases in abdominal adiposity **(Wirshing, Spellberg et al. 1998)**. Weight gain is unlikely to be the sole etiology of glucose dysregulation induced by the SGA , as glucose dysregulation has occurred in both the presence **(Wirshing, Spellberg et al. 1998; Wehring, Alexander et al. 2000; Ananth, Gunatilake et al. 2001)** and absence of weight gain **(Mallya, Chawla et al. 2002; Ramankutty 2002)**. Likewise,

glucose dysregulation has been noted to resolve, in some cases rapidly, on discontinuation of the antipsychotic but without necessarily an accompanying decrease in weight. Irrespective of the mechanism by which glucose dysregulation occurs, it may have significant short and long terms sequel for clients health.

Chapter 3
Research Design and Methods

3.1 Study design and Site of the Study

A cross sectional study conducted from August 2011 until February 2012 at governmental primary healthcare psychiatric centers in Northern West-Bank (Nablus, Jenin, Tulkaram, Qalqilai).

3.2 Inclusion Criteria

All clients attending the above mentioned psychiatric healthcare centers during the study period with the following criteria were invited to participate:

1) Their age was above 16 years old.

2) They were diagnosed with schizophrenia as defined by Diagnostic and Statistical Manual Mental Disorder (DSM-IV).

3) They had not been suffering from an acute attack of illness during the last year.

4) Their drug regimen had not been changed in the last 6 months

3.3 Exclusion Criteria

Patients who had the following characteristics were excluded from the study:

1) Newly diagnosed patients
2) Clients with current acute psychiatric episode or relapse
3) Schizophrenic clients who are not on antipsychotic medications

3.4 Sampling Method and Sample size

A convenience, non-probability, sampling method was used. In order to estimate with sufficient precision the prevalence of pre-DM, it was hypothesized that the prevalence of pre-DM in the general population to be 10%. We calculated the sample size with a 99% confidence interval and of a 10% width. Based on this, we needed a sample size of approximately 240 clients currently attending the governmental primary psychiatric healthcare centers in North West - Bank.

3.5 Data Collection

Data collection form was developed to cover all data items needed. The form covered the following areas: socio-demographic details, employment, length of psychiatric illness; pharmacological treatment currently used; history of psychiatric hospitalization, body weight, height, waist circumference, FBG measured in mg/ dL and HbA1c.

3.6 Tested Variables

1. **Pre-DM and DM:** The definition of normal and impaired fasting glucose (pre-DM) differs between WHO and that of the American Diabetes Association (ADA). The WHO kept its upper limit of normal FBG at under 110 mg/dL for fear of causing too many people to be diagnosed as having impaired fasting glucose, whereas the ADA lowered the upper limit of normal to a fasting glucose under 100 mg/dL (Table 3.1)

2. **Weight and Height**: They were measured with the participant in standing position without shoes and heavy garments and recorded to the nearest kilogram, and full centimeter (cm). Electronic balance scales were used. The zero level was checked every day before starting measurements and immediately afterwards. Waist circumference was measured in centimeters using the meter scale. Body mass index was calculated using the known equation.

$$\mathrm{BMI} = \frac{\mathrm{mass(kg)}}{\mathrm{(height(m))^2}}$$

3. **Waist circumference (WC). It was measured and recorded to the nearest centimeter.** The WC was considered normal when the value was less than 102 cm for men and less than 88 cm for women. This is

based on the Adult Treatment Panel III guidelines for definition of metabolic syndrome **(NCEP) 2002; Fedder, Koro et al. 2002)**.

4. **FBG and HbA1c:** Blood samples were collected from all subjects between 8:00 and 9:00 (A.M.) after 12 hours overnight fast. Blood was collected from an ante-cubital vein punctures and was collected while client in a sitting position. FBG was determined using Chemistry kits bought from Human, Germany while HbA1c determination was done using a kit from Vital Diagnostics, USA.

5. **Dysglycemia** was defined as FBG ≥ 110 mg/ dL. Therefore clients with either Pre-DM or DM were considered to have dysglycemia. Euglycemia was defined as FBG < 110 mg / dl

6. **Insulin resistance**: Insulin resistance defined as TG/ HDL > 3 **(McLaughlin, Abbasi et al. 2003; McLaughlin 2003; McLaughlin, Allison et al. 2004; McLaughlin, Reaven et al. 2005)**

7. Triglycerides and High-density lipoprotein: Blood samples were collected from all subjects between 8:00 and 9:00 (A.M.) after 12 hr overnight fast. Values for HDL-C was divided according to the following categories: less than 40 mg/ dl (low); 40 – 60 mg/ dl (medium); and more than 60 mg/ dl is considered high . Values for TG were classified according to the following categories: less than 150 mg/ dl (normal); 150.1 – 200 mg/ dl (borderline high); High level and very high is greater than 200mg/dl.

8. **Independent Variables***:* Independent variables include age, gender, number of years of education, place of residence (city, village or camp), marital status (married, single and divorced), smoking, duration of the psychiatric illness, number of psychiatric hospitalizations, body weight (in kilograms), height in (meter), waist circumference (in cm), occupation and family history of diabetes and other chronic illnesses.

9. **Chlorpromazine Dose Equivalencies (CPZeq)**

   Type and dose of antipsychotic medications used by the patients were collected from the patients' medical records. The daily dose of antipsychotic medication prescribed to each patient was converted to milligram equivalents of chlorpromazine according to conversion factors derived from the literature **(Woods 2003; Xiang, Weng et al. 2008; Joseph. Dipiro, Robert L. Talbert et al. 2011)**. Daily doses of antipsychotics, including depot antipsychotics, were converted to approximate chlorpromazine equivalents (CPZeq) using published guidelines **(Shen 2002; Woods 2003)**. The CPZeq is a measure of the relative antipsychotic potencies of neuroleptics. They are generally expressed as a ratio, relative to the arbitrary value of 1, which corresponds to the antipsychotic effects of chlorpromazine. For example, an antipsychotic drug with a CPZeq value of 100 would be 100 times more potent than chlorpromazine.

10. Total CPZeq dose

Total CPZeq dose is defined as the aggregate dosage of antipsychotic medication prescribed in CPZ units. It is constructed by calculating a total daily dose of each antipsychotic listed in the discharge summary, converting that total into CPZ units for each antipsychotic by multiplying the antipsychotic-specific conversion factor and the antipsychotic daily total. Then each converted antipsychotic-specific CPZ amount is added to arrive at a total dose.

11. Combination and monotherapy

The operational definition of antipsychotic drug monotherapy is the use of one antipsychotic drug while antipsychotic drug combination is the use of two or more antipsychotic drugs.

12. FGA versus SGA

For this study, the following drugs were considered FGA: Butyrophenones (Haloperidol, Droperidol); Phenothiazines (Chlorpromazine, Fluphenazine, , Thioridazine, Trifluoperazine, Promethazine, Pimozideand and Thioxanthenes Chlorprothixene, While the following drugs were considered SGA: Clozapine, Quetiapine, Risperidone, Ziprasidone olanzapine.

3.7 Data Analysis

Descriptive statistics for all study variables were computed. These descriptive statistics included frequencies and percentages for all categorical variables in addition to means, standard deviations and ranges not all continuous variables. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS; version **18.0**) for Windows. The conventional 5 percent significance level was used throughout the study. The median (Q1-Q3)was used for duration of psychiatric illness .Also spearman correlation was used in the results. Research questions and analytical methods used for each research question are shown in Table 3.2.

3.8 Ethical Consideration

Approval to perform the study was obtained from the Palestinian ministry of health and the college of Graduate Studies at An-Najah national University and Institutional Review Board (IRB).

Table 3-1 The definition of normal and impaired fasting glucose (pre-DM) based on WHO and ADA criteria.

Diabetic Category	WHO (World Health Organization. "Definition 2007)	ADA (ADA 2011)
Diabetic	FBG≥ 7.0 mmol/l (126 mg /dl) HBA1C ≥ 6.5%	FBG≥ 126mg/dl (7.0 mmol/l) HbA1C ≥ 6.5 %
Pre diabetic	FBG6.1 to 6.9 mmol/l (110 mg/dl to 125 mg /dl)	FBG100 to 125 mg /dl (5.6 to 6.9 mmol/l) HbA1C (5.7 to 6.4 %)
Normal	FBG< 6.1 mmol/l (110 mg/dl)	FBG< 100 mg/dl (5.6 mmol/l) HbA1C < 5.7 %

Table 3-2 the research questions investigated, hypothesis for each research question, variables tested and analytic technique used in testing the hypothesis.

Research Question	Hypothesis	Tested Variables	Analytic technique
What is the mean FBG and the prevalence of pre-DM and DM among the study sample?	1. The mean FBG among the study sample is not significantly different from that of the general population	Mean FBG for general population	One sample T test
Is the prevalence of pre-diabetes in schizophrenic clients higher than that reported in general population?	There is no difference in the prevalence of pre-DM between clients with schizophrenia and the general population.	Prevalence of pre-DM in the study sample, Prevalence of pre-DM) in the general population	Binomial Chi square test
Is the prevalence of DM in clients with schizophrenia higher than that reported in general population?	There is no difference in the prevalence of DM between clients with schizophrenia and that reported in general population.	Prevalence of DM in the study sample, Prevalence of DM in the general population	Binomial Chi square test
What are the demographic and clinical predictors of dysglycemia?	There are no significant predictors of dysglycemia among schizophrenic clients.	Dependent variable: dysglycemia Independent variables: Age Gender BMI WC Duration of the disease Family history of DM CPZ equivalent Maximum % of BNF dose Polypharmacy Depot medication Anticholinergic Type of antipsychotic drug	Univariate analysis and Multiple logistic regression

Chapter 4
Results

4.1 General descriptive statistics of the study sample

During the study period, 250 met the inclusion criteria and were investigated. Of the 250 clients, 68 (27.2%) were female and 182 (72.8%) were male clients. The mean age of the clients was 41.9 ± 11.8 [95% CI: 40.5 – 43.4; range: 54] years. No significant difference in age was found between male and female clients (40.3 ± 12.4 for females versus 42.5 ± 11.5 years for males; $p = 0.2$). Approximately half of the clients came from villages (145, 58%) while the remaining (105, 42%) came from city or camps. The majority of the clients [213 (85.2%)] had less than high school education and more than half (153; 61.2%) were smokers. The majority of the clients (197; 78.8%) were unemployed. More than half (138; 55.2%) of the clients were either unmarried or divorced.

The median for the duration of psychiatric illness in the sample was 15 years (Q1 – Q3: 9 - 20 years). The mean number of psychiatric hospitalization of the clients during their lifetime was 1.9 ± 3.2, range: 0 – 20 times, and 95% CI was 1.5 – 2.3. Based on normal values for (WC); 56 (82.4%) female clients had WC above the normal value while only 58 (31.9%) male clients had a WC above the normal value. Abdominal obesity was significantly associated with females ($p < 0.01$). Details regarding

basic demographic and clinical characteristics of the clients are shown in Table 4-1.

4.2 Results regarding research question number 1

The mean FBG and prevalence of pre-diabetes and diabetes mellitus among the study sample?

1. The mean FBG of the schizophrenic clients was 99.5 ± 47.5 mg/ dL (95% CI 93.5 – 105.4). The mean FBG in the study sample was significantly higher than that reported in the general population (99.5 versus 92.8 mg/ dL; p <0.001) (Kharobi et al, 2012, personal communication).

2. The mean HbA1c value of the study sample was 5.6 ±1.1% (95% CI 5.5 – 5.7). The minimum was 3.5% and maximum was 11,%.

3. There was a significant correlation between FBG, HbA1c and insulin resistance markers as shown in table 4.2. The significant correlation between HbA1c and FBG and insulin resistance markers is suggestive of the accuracy of the data. .

4.3 Results regarding research question number 2 and 3:

The prevalence of IGR (pre-diabetes) and diabetes mellitus among clients with schizophrenia?

1. Based on WHO and ADA criteria, 27 clients (10.8%) had a FBG ≥ 126 mg/ dL (diabetic).
2. Based on ADA criteria of HbA1c, there were 26 (10.4%) whose HbA1c ≥ 6.5% (diabetic).
3. Based on WHO classification, 34 (13.6%) clients had FBG between 110 – 125 mg/ dL (pre-diabetic).
4. Based on ADA criteria, 53 (21.2%) had a FBG from 100 – 125 mg/ dl (pre-diabetic).
5. Based on ADA criteria, there was 70 (28%) whose HbA1c was between 5.7 – 6.4% (pre-diabetic).

For comparison of prevalence of pre-diabetes in schizophrenia clients and general population, we used the WHO criteria because previously published studies about pre-diabetes and DM in Palestine used the WHO criteria. In this study, the prevalence of pre-DM, but not DM, was significantly higher than that reported in different studies carried out in Palestine shown in Table 4-3

4. 4 Results regarding research question number 4:

What are the demographic and clinical factors associated with dysglycemia (pre-diabetes and DM) among schizophrenic clients?

1. There was 189 (75.6%) clients with euglycemia and 61 (24.4%) with dysglycemia. Levels of FBG, HbA1c and insulin resistance marker (TG/HDL) for clients with dysglycemia and euglycemia are shown in Table 4-4

2. Univariate analysis showed that the following variables were significantly associated with dysglycemia: gender, age, waist circumference, duration of the illness, use of depot antipsychotics, use of anticholinergics, use of combination antipsychotics, and dose of antipsychotics as measured by CPZeq shown in Table 4-5.

3. All variables that had significant associations with dysglycemia in univariate analysis were entered into multiple logistic regressions to find out significant predictors of dysglycemia among schizophrenic clients shown in Table 4-6.
4. Multiple logistic regression showed that only advancing age and waist circumference (normal or higher than normal) were the only significant predictors of dysglycemia among clients with schizophrenia.

Table 4-1 Demographic characteristics of the study sample

Variable	Statistics
Gender	
- Male	182 (72.8%
- Female	68 (27.2%)
Age (years)	41.9 ± 11.8
Age category	
- Less than 30	43 (17.2%)
- 30 – 40	76 (30.4%)
- 40 – 50	80 (32%)
- > 50	51 (20%)
Residence	
- City	105(42%)
- Village/ Camp	145 (58%)
Education	
school education or less	213 (85.2%)
College education	37 (14.8%)
Marital Status	
Single/ Divorced	138 (55.2%)
Married	112 (44.8%)
Smoker	
Yes	153 (61.2%)
No	97 (38.8%)
Occupation	
Not working	197 (78.8%)
Working	53 (21.2%)
Duration of psychiatric illness (years)	15 (Q1 – Q3: 9 – 20)
≤ 10 years	89 (35.6%)
> 10 years	161 (64.4%)
Number of psychiatric hospitalization	1 (Q1 – Q3: 0 – 2)
Waist Circumference (cm)	
- Male	98 ±14.1
- Female	102.2 ± 12.4
Abnormal Waist Circumference	
Male	58/ 182 (31.9%)
Female	5/68 (82.4%)

Table 4.2 Spearman correlation between FBG, HbA1c and insulin resistance among schizophrenic clients

	FBG	**HbA1c**	**TG/HDL**
FBG	-------	r = 0.22; p< 0.01	r = 0.16; p=0.01
HbA1c	r = 0.22; p< 0.01	-------	r = 0.19; p<0.1
TG/ HDL	r = 0.16; p=0.01	r = 0.19; p< 0.01	-------

Table4.3: Prevalence of pre-DM and DM in the current study compared with the published values in the general population.

Criteria	Normal	Pre-diabetes			Diabetes Mellitus			Dysglycemia
		Current Study	Reported data (ref)	P	Current study	Reported data (ref)	P	
FBG (WHO)	189 (75.6%)	34 (13.6%)	5.9%(Abdul-Rahim, Husseini et al. 2001)	<0.01	27 (10.8%)	12%(Abdul-Rahim, Husseini et al. 2001)	0.6	24.4%
			8.6%(Husseini, Abdul-Rahim et al. 2000)	<0.01		10%(Husseini, Abdul-Rahim et al. 2000)	0.7	
			8.9%*	<0.01		11%(Shaw, Sicree et al. ; WHO/DM/Report)	0.9	
FBG (ADA)	170 (68%)	53 (21.2%)	-	-	27 (10.8%)	-		32%
HbA1c (ADA)	154 (61.6%)	70 (28%)	-	-	26 (10.4%)	-		38.4%

*** : Personal Communication from Kharoubi et al (2012) .**

Table 4-4 Descriptive statistics of glucose metabolism in the study sample.

Variable	Euglycemia	Dysglycemia
HbA1c (%)	5.34 ± 0.7	6.2±1.8
FBG (mg/dL)	82.1±12.5	153.5±70.3
TG/ HDL	4.4±4.3	5.3±3.7

Table 4- 5 Univariate analysis of dysglycemia

Variable	Reference category	B	P	O.R	95% CI
Gender	Female	- 0.8	0.015	2.1	1.2 - 4
Age	Continuous variable	0.055	00.00	1.1	1.02 - 1.09
Education	School education	0.2	0.7	1.2	0.52 - 2.8
Marital status	Single	0.32	0.3	1.4	0.8 - 2.5
Smoking	Not smoking	0.3	0.32	0.74	0.4 - 1.33
Occupation	Not working	0.78	0.12	0.42	0.4 - 1.3
Waist circumferences	Normal WC	1	0.001	2.7	1.5 - 4.9
Duration of the psychiatric illness	< 10 years	1.03	0.004	2.8	1.4 - 5.6
Number of hospitalization	< 2	0.6	0.124	1.6	0.9 – 2.9
Family history of DM	No family history	0.06	0.84	1.1	0.6 - 1.9
use Depot medication antipsychotic	No depot medication	0.7	0.031	1.9	1.06 - 3.6
Anticholinergic	No anticholinergic drugs	1	0.01	2.6	1.2 - 5.5
SGA	No SGA	-0.21	0.6	0.8	0.4 - 1.7
Combination therapy	Monotherapy	0.64	0.034	1.9	1.1 - 1.34
CPZ eq	Continuous variable	0.7	0.034	2	**2.1** - 3.8

Table 4-6 Univariate analysis.

Variables	B	Sig.	Exp(B)	95.0% C.I.for EXP(B)
Gender	-.639-	.108	.528	.242 - 1.151
Age	.054	.003	1.055	1.018 -1.093
Waist circumference category	.938	.013	2.556	1.214 - 5.379
Duration of psychiatric illness category	.111	.810	1.118	.451 - 2.771
Depot injection	.190	.627	1.209	.563 - 2.597
Anticholinergic drug	.669	.132	1.952	.817 - 4.667
Mono Therapy	.266	.558	1.304	.537 - 3.169
Total CPZ drug	.001	.363	1.001	0.999-1.002

Chapter 5
Discussion

5.1 Discussion

We investigated and compared the prevalence rates of pre-DM and DM among schizophrenia clients with those reported in the general Palestinian population. Our study showed that schizophrenia clients had a similar prevalence of DM but a significantly higher prevalence of pre-DM compared to the general population of Palestine **(Shaw, Sicree et al. ; Husseini, Abdul-Rahim et al. 2000; Abdul-Rahim, Husseini et al. 2001)**. Because our study is a cross sectional study, we were unable to establish that the increased rates of pre-DM were caused by antipsychotic treatment.

Initial evidence from samples of patients treated in the early 1990s, before the advent of new antipsychotic agents, suggests that people with schizophrenia are more likely to develop glucose dysregulation than those in the general population **(Dixon, Weiden et al. 2000)**. Studies have also shown that psychotic symptoms are related to increased rates of DM in nonclinical samples, independent of several potential confounders—including a clinical diagnosis of psychosis or schizophrenia, previous antipsychotic treatment, depression, lifestyle, and individual or country socioeconomic status **(Nuevo, Chatterji et al. 2003)**.

Our cross-sectional study found a 10.8% and 13.6% prevalence of DM and pre-DM respectively among people with schizophrenia. Data regarding prevalence of DM in our study is close to earlier reports, including the 13% prevalence of DM found in the CATIE study **(Goff, Sullivan et al. 2005)** and other studies reported in American and European patients with schizophrenia **(Mukherjee, Decina et al. 1996; Dixon, Weiden et al. 2000; Lindenmayer, Czobor et al. 2003; Ryan, Collins et al. 2003)**. The prevalence of DM reported in our study was higher than that reported in Taiwanese schizophrenia study (7.9%) **(Chien, Hsu et al. 2009)** and a study in France (2.2%) **(Philippe, Vaiva et al. 2005)**.

Our study has important implications for clinical practice and future research. The high prevalence of pre-DM underscores the importance of routine FBG monitoring of patients with psychotic symptoms or those treated with antipsychotics. Cardiovascular risk factors such as DM hypertension and dyslipidemia commonly coexist **(Mukherjee, Decina et al. 1996)**. So, it seems likely that those people with dysglycemia may also have co-morbidities that further increase their risk of cardiovascular disease and premature death **(Subramaniam, Chong et al. 2003)**. The strength of the association between schizophrenia and DM is such that timely screening and effective management of DM risk factors in all our clients is recommended. Early detection of pre-DM and effective education about healthy living should help to reduce the risk of patients developing diabetes and its complications, and may ultimately help to improve long-term

outcomes. The most recent position statement from the American Diabetes Association (ADA) regarding diabetes screening include risk factors like family history of a first-degree relative with type II DM, being overweight, habitual physical inactivity, particular races/ethnicities (eg, African Americans, Hispanic Americans, Native Americans), previously identified impaired fasting glucose or glucose tolerance, hypertension (>140/90 mm Hg or taking medication for hypertension), high-density lipoprotein cholesterol <35 mg/dL and/or triglyceride level >250 mg/dL are associated with insulin resistance **(ADA 2011)**. Assuming the ADA risk factors are representative of patients diagnosed with schizophrenia in general, the high prevalence of risk factors for diabetes is likely part of the explanation for the high prevalence of dysglycemia in our sample, regardless of the external variable of antipsychotic exposure.

The univariate analysis in the current study indicated that the following variables were significantly associated with dysglycemia: female gender, advancing age, abdominal obesity measured as waist circumference, duration of psychiatric illness, use of depot medications, use of anticholinergics drugs, use of combination therapy, and use of higher dose of antipsychotic agents measured in CPZeq. However, only advancing age and waist circumference were the only significant predictors of dysglycemia in schizophrenia clients. Current literature does not provide a clear understanding of which risk factors best predict the development of dysglycemia in patients with schizophrenia. Our analysis suggests that

presence of primary risk factors is more important than exposure to antipsychotic agents in the development of dysglycemia in patients with schizophrenia.

Regression analysis suggested that female gender was not a significant factor associated with dysglycemia in schizophrenia clients. However, previous reports suggested an increased prevalence of antipsychotic-associated diabetes among women treated with first generation typical antipsychotic drugs **(Dixon, Weiden et al. 2000)** while other studies have not found gender as a risk factor for antipsychotic-associated diabetes **(Lamberti, Costea et al. 2005)**. It is speculated that antipsychotic associated DM in schizophrenia might be influenced by hormonal development of DM. A recent study in humans shows that female sex hormones may play an important role in the pathogenesis of IFG and IGT, both of which are known to increase the risk of developing diabetes **(van Genugten, Utzschneider et al. 2006)**.

Our study showed that advancing age and higher waist circumference are significantly associated with dysglycemia. One study evaluated risk factors for DM in patients with schizophrenia and found that risk factors for DM in schizophrenia are similar to those in the general population **(Dixon, Weiden et al. 2000)**. In our study, age was a significant risk factor for dysglycemia (FBG > 110 mg/ dL) which is similar to that observed in other studies **(Dixon, Weiden et al. 2000; Subramaniam, Chong et al. 2003; Hung, Wu et al. 2005; Philippe,**

Vaiva et al. 2005). This association might be expected given that DM incidence increases with age. Furthermore, the duration of antipsychotics use among schizophrenic clients is associated with increasing age. Another risk factor that was significantly associated with dysglycemia was abnormal waist circumference. It should be mentioned that some antipsychotic agents may contribute to weight gain and thus indirectly contribute to abnormal waist circumference. Effects of antipsychotic treatment on intra-abdominal fat have been shown to be inconsistent in current available literature. Further clouding the picture is a body of evidence showing the presence of increased intra-abdominal and visceral fat in the absence of antipsychotic treatment in patients with schizophrenia, indicating that the presence of schizophrenia itself may be associated with increased intra-abdominal fat stores **(Thakore, Mann et al. 2002; Ryan, Flanagan et al. 2004)**. Other studies reported similar findings regarding association of obesity and DM in schizophrenic clients **(Tabata, Kikuoka et al. 1987; Sernyak, Gulanski et al. 2003; Cavazzoni, Mukhopadhyay et al. 2004; Hung, Wu et al. 2005)**. Our study showed no significant association between family history of DM and dysglycemia. This is in contrast to results reported by other researchers **(Hung, Wu et al. 2005; Lamberti, Costea et al. 2005)**. Our data showed no significant association with the type of antipsychotic (FGA versus SGA) in contrast to other reported studies **(Sernyak, Leslie et al. 2002)**. This discrepancy, however, could be explained in terms of the population characteristics — longer duration of illness, the cumulative effects of both FGA and SGA used

over the preceding years, and the confounding effect of concurrent psychotropic drug use. These findings suggest that the pathophysiology of schizophrenia–diabetes comorbidity is far more complex than originally speculated **(Cohen, Stolk et al. 2006)**. Furthermore, the smaller sample size of patients using SGA in our study might be the reason for not detecting such difference.

The fact that there is a significant association between dysglycemia and modifiable risk factor such as abdominal obesity (WC) may facilitate the development of appropriate preventive strategies. Interventions focused on preventing diabetes as opposed to treating this metabolic condition and its complications once they are present, will not only reduce costs but will provide sufferers with the most effective tools for maintaining and improving their health and well-being. Our study showed that there was a significant association between the duration of illness and prevalence of dysglycemia. A higher prevalence of dysglycemia has been reported when patients are treated for a longer duration **(De Hert, van Winkel et al. 2006; Srisurapanont, Likhitsathian et al. 2007)**.

Finally, the odds of being prescribed higher antipsychotic doses were higher among patients with dysglycemia than those without diabetes. However, meta-analytic reviews suggest that the association between atypical antipsychotics and diabetes risk remains controversial because of the poor methodological quality in most studies **(Smith, Hopkins et al. 2008; Okumura, Misawa et al. 2010)**. Furthermore, although little is

known about the risk of diabetes during antipsychotic treatment in patients with preexisting diabetes, one case–control study indicated that the new use of both conventional and atypical antipsychotics is associated with a significant increase in hospitalization for hyperglycemia among patients with preexisting diabetes (RR, 1.50; 95% CI,1.29–1.74)**(Lipscombe, Levesque et al. 2009)**. Therefore, considering the fact that the odds of being prescribed conventional antipsychotics are higher among patients with diabetes, it is necessary to further investigate whether such practices are somewhat reasonable.

5.2 Limitation of the Study

Our analyses had a number of limitations. First, the cross-sectional nature of this study limits the ability to establish a relationship of antipsychotic drug exposure to the development of diabetes. In addition, there is a possibility for bias in examining drug exposure because a drug may have been administered after diabetes was diagnosed. Lastly, the sample size that we enrolled was small which may have limited our ability to detect other statistically significant risk factors associated with diabetes. Second, the medical chart data may have been inaccurate or incomplete, and there may have been misclassification in the identification of diabetes..Third potential limitation of this study is the use of discharged patients with schizophrenia, which may limit generalizability of the results to those patients who undergo long-term hospitalization, those who are

treated on outpatient department basis, and those who do not come for treatment.

5.3 Conclusion

This study confirmed the high prevalence of dysglycemia among clients diagnosed with schizophrenia, supporting the need for enhanced monitoring for diabetes in this population. It also helped to confirm a high prevalence of risk factors in people with schizophrenia. Risk factors for diabetes in this sample identified by univariate anlyses indicated that the following variables were significantly associated with dysglycemia: female gender, advancing age, abdominal obesity measured as waist circumference, duration of psychiatric illness, use of depot medications, use of anticholinergics, use of combination therapy, and use of higher dose of antipsychotic agents measured in CPZeq. However, only advancing age and waist circumference were the only significant predictors of dysglycemia in schizophrenia clients. Though it is difficult to establish causation due to the cross-sectional nature of the study, these risk factors are consistent with current knowledge about diabetes risk factor and metabolic effects of antipsychotic drugs.

It is likely that the presence of primary risk factors is more important in the development of type 2 DM in patients with schizophrenia than exposure to antipsychotic drugs whatever the mechanism by which the increased risk of diabetes occurs, people with schizophrenia have been

shown to be more likely to develop type 2 DM than those in the general population. The development of appropriate screening guidelines will help clinicians decide which patients are at greatest risk of developing type 2 DM and ensure that the frequency of type 2 DM screening is adequate to reduce associated morbidity and mortality. These screening guidelines should include assessment of advancing age and waist circumferences , both of which appear to be strongly associated with increased risk of diabetes in patients with schizophrenia.

Recommendations:

1- Importance of routine fasting plasma glucose monitoring of patients with schizophrenia or those treated with antipsychotic.

2-Effective management of diabetes risk factors in all our patients is recommended.

3- Early detection of pre-DM and effective education about healthy living should help to reduce the risk of patients developing diabetes and its complications.

4-The development of appropriate preventive strategies for diabetes .

5- Applying appropriate prescribing pattern of antipsychotic medication.

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Appendices

Data collection sheet

NO.....

Diaphragmatically Data

1. Name .....
2. Age: .....
3. Location ☐ City ☐ Village ☐ Camp .....
4. Education ☐ Elementary ☐ Secondary ☐ Diploma ☐ B.A
5. Material Status: ☐ Married ☐ Single ☐ Divorce
6. Smoker ☐ yes ☐ no
7. Occupation: ☐ employee ☐ labor ☐ non
8. Type of job: .....
9. File number in clinic.....

Physical Data:

- Weight .....
- Height .....
- Waist circumstances: .....
- BP.....

History of Mental Illness:

1. Diagnosis .....
2. Duration of the disorder.....
3. How many times admitted to hospital.....

Medical history for clients and family:

1. .....
2. .....
3. .....
5. Any body in family have DM (Yes, No).
6. Any body in family have problem in lipid (Yes, No).
7. Any body in family have problem in renal function (Yes, No).
8. Do you take any antibiotic now (Yes, No).

Drug profile:

Drug Name	Strength	Route	Frequency	Duration

جامعة
النجـــاح الوطنية
كلية الدراسات العليا
مكتب العميد

An-Najah
National University
Faculty of Graduate Studies
Dean's Office

التاريخ : 2011/5/3

حضرة الدكتورة عائدة القيسي المحترمة
منسق برنامج ماجستير تمريض الصحة النفسية والمجتمعية

تحية طيبة وبعد،

الموضوع : الموافقة على عنوان الاطروحة وتحديد المشرف

قرر مجلس كلية الدراسات العليا في جلسته رقم (234)، المنعقدة بتاريخ 2011/4/7، الموافقة على مشروع الأطروحة المقدم الطالب / صلاح علي ابراهيم دلال، رقم تسجيل 10953932، تخصص ماجستير تمريض الصحة النفسية المجتمعية، عنوان الأطروحة:

(مدى انتشار عدم انتظام نسبة السكر في الدم عند مرضى الشيزفرينيا في شمال الضفة الغربية)
(Prevalence of Impaired Glucose Regulation (IGR) Among Schizophrenic Clients in Northern West Bank)

بإشراف : 1- د. وليد صويلح 2- د. اياد علي

يرجى اعلام المشرف والطالب بضرورة تسجيل الاطروحة خلال اسبوعين من تاريخ اصدار الكتاب. وفي حال عدم تسجيل الطالب/ة للاطروحة في الفترة المحددة له/ا ستقوم كلية الدراسات العليا بإلغاء اعتماد العنوان والمشرف.

وتفضلوا بقبول وافر الاحترام ،،،

عميد كلية الدراسات العليا

د. محمد أبو جعفر

نسخة : د. رئيس قسم الدراسات العليا للعلوم الطبيعية المحترم
: ق.أ.ع. القبول والتسجيل المحترم
: مشرف الطالب
: الطالب
: الملف

03-05-2011

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An-Najah
National University
Faculty of Medicine

بسم الله الرحمن الرحيم

جامعة
النجاح الوطنية
كلية الطب

IRB Approval letter

Study title:
Prevalence of impaired glucose regulation (IGR) among schizophrenic clients

Submitted by:
Salah Dalal & Waleed M.Sweileh

Date Reviewed:
April 26, 2011

Date approved:
April 27, 2011

Your study titled" Prevalence of impaired glucose regulation (IGR)among schizophrenic clients . "Was reviewed by An-Najah National University IRB committee & approved on April 27, 2011.

IRB

IRB Committee Chairman,
An-Najah National University
Samar Musmar,MD, FAAFP

نابلس - ص.ب ٧٠٧,٧ هاتف: ٠٩-٢٣٤٢٩٠٢/٤/٧/٨/١٤ (٠٩)(٩٧٢)، فاكسميل ٠٩-٢٣٤٩٧٣٩ (٠٩)(٩٧٢)
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السلطة الوطنية الفلسطينية
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Palestinian National Authority
Ministry of Health - Nablus
General Directorate of Higher & Continuing Education

الرقم: ...
التاريخ: ...

Ref.: .....
Date: .....

الأخ مدير عام الرعاية الصحية الأولية والصحة العامة المحترم،،،

تحية واحترام،،

الموضوع: تسهيل مهمة طلاب – جامعة النجاح الوطنية

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مع الجامعات والمؤسسات الأكاديمية بإتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسسات الوطنية وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة طلاب ماجستير الصحة النفسية/ جامعة النجاح الوطنية التالية اسماؤهم بعمل مقابلات مع مرضى الصحة النفسية في عيادات (طولكرم، نابلس، قلقيلية، جنين) وسحب دم لمرضى القصام العقلي:

1- سامي شاكر العيويني	**Among prevalence of dyslipidemia schizophrenic client in northern West Bank**
2- هشام زاهر زهران	**Blood profile of selected schizophrenic client in northern Palestine**
3- صلاح علي دلال	**Prevalence & imperial glucose resolution (IGR) among schizophrenic client**
4- جهاد محمد يتي عودة	**Prescribing pattern of antipsychotic schizophrenic client in northern Palestine**

- شريطة
- موافقة المرضى أو ذويهم.
- الحفاظ على سرية معلومات المرضى
- موافاتنا بنسخة من نتائج البحث.

مع الاحترام،،

الدكتور سعيد الهموز
مدير عام التعليم الصحي

وارد
2011

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جامعة النجاح الوطنية
كلية الدراسات العليا

انتشار خلل تنظيم الجلوكوز (IGR) عندمرضى الفصام العقلي في شمال الضفة الغربية

إعداد
صلاح علي دلال

أشراف
أ.د. وليد صويلح
د. اياد العلي

قدمت هذه الأطروحة استكمالاً لمتطلبات درجة الماجستير لتخصص تمريض الصحة النفسية المجتمعية بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس – فلسطين .

2012

انتشار الخلل في تنظيم الجلوكوز لدى مرضى الفصام العقلي في شمال الغربية

إعداد

صلاح علي دلال

إشراف

أ.د وليد صويلح

د. إياد علي

الملخص

الخلفية والأهداف:هو معرفة مدى انتشار الخلل في تنظيم الجلوكوز لدى مرضى الفصام العقلي ومقارنته مع عموم السكان.

المنهجية: نفذت هذه الدراسة في أربعة مراكز للرعاية الصحية الأولية الحكومية للأمراض النفسية في شمال الضفة الغربية (نابلس, جنين, طولكرم, قلقيلية). حيث تم قياس نسبة الجلوكوز في الدم وتم أيضا قياس معدل الجلوكوز التراكمي أثناء الصيام. وقد استخدمت معايير منظمة الصحة العالمية وجمعية السكري الأمريكية من اجل تعريف الخلل في تنظيم الجلوكوز في الدم. حيث تم تعريف الخلل في تنظيم الجلوكوز عندما تكون نسبة الجلوكوز للمريض الصائم أكثر من 110 ملغم / ديسلستر.

النتيجة: بناء على معايير منظمة الصحة العالمية تبين أن 27 مريض (10.8%) يعانون من مرض السكري وان 34 مريض (13.6%) يعانون من انتشار مرحلة ما قبل السكري .وان نسبة مرض السكري لا تختلف كثيرا عن عموم السكان في فلسطين ولكن انتشار مرحلة ما قبل السكري أعلى من عموم السكان في فلسطين. وأظهرت التحاليل الإحصائية أن العمر ومحيط الخصر كانت من أهم العوامل التي تدل على الخلل في تنظيم الجلوكوز عند مرضى الفصام العقلي.

الخلاصة :هذه الدراسة تؤكد ارتفاع معدل انتشار الخلل في تنظيم الجلوكوز لدى مرضى الفصام العقلي. وان هذه النتائج تؤكد الحاجة إلى تعزيز الرصد لهذا الخلل عند مرضى الفصام العقلي. فمن

المرجح أن وجود عوامل الخطر الأساسي هو أكثر أهمية في تطوير الخلل في تنظيم الجلوكوز أكثر من التعرض لأدوية المضادة للذهان.