Diabetes mellitus in patients with schizophrenia in West-Bank, Palestine


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**Article Info**

Article history:
Received 24 June 2012
Received in revised form
22 November 2012
Accepted 17 December 2012

Keywords:
Pre-diabetes mellitus
Diabetes mellitus
Palestine
Schizophrenia

**Abstract**

Aims: The main aims of the study were to investigate the prevalence of pre-diabetes and diabetes mellitus (DM) in patients with schizophrenia, to compare it with those published in the general population, and to assess significant associations with dysglycemia defined as having either pre-DM or DM.

Methods: A cross-sectional study carried out in 4 governmental primary psychiatric healthcare centers in Northern West-Bank, Palestine. Fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) were measured. The World Health Organization (WHO) criteria for defining pre-DM and DM were used. Dysglycemia was defined as FBG >110 mg/dl.

Results: Based on WHO criteria, 27 patients (10.8%) had diabetes and 34 (13.6%) had pre-diabetes. The prevalence of DM in patients with schizophrenia was not significantly higher than that reported in the general population of Palestine. However, the prevalence of pre-DM was significantly higher than that reported in the general population of Palestine. Regression analysis showed that advancing age and abnormal waist circumference were significant predictors of dysglycemia in patients with schizophrenia.

Conclusions: This study confirmed the high prevalence of dysglycemia in patients with schizophrenia, supporting the need for monitoring of blood glucose in this category of patients. The presence of primary risk factors is more important in the development of dysglycemia in patients with schizophrenia than exposure to antipsychotic drugs.

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1. Introduction

Schizophrenia is a mental disorder that affects approximately 1% of populations throughout the world [1–3]. Antipsychotic drugs are the mainstay therapy for schizophrenia. People diagnosed with schizophrenia are at an increased risk of diabetes mellitus (DM) and this risk is more common among patients treated with second-generation antipsychotic (SGA) agents [4,5]. Studies in developing countries indicated that Type 2 DM has an estimated prevalence of 4.5% in the general population and 16–25% in patients with schizophrenia [6,7]. This metabolic adverse effect has significant implications in terms of both the cost of treatment and the disease burden for patients with mental illness. The exact mechanism of antipsychotic induced glucose dysregulation is not well understood. One possible mechanism 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 [8]. Another mechanism of antipsychotic-induced diabetes is due to weight gain, which can lead to insulin resistance and hyperglycemia [9]. Second generation antipsychotic drugs such as olanzapine and clozapine are associated with higher risk of weight gain [10].

Intermediate hyperglycemia or pre-diabetes represents an intermediate metabolic stage between normal glucose homeostasis and DM. Pre-diabetes can progress to DM and is also
increases mortality rates [11]. Studies on glucose disorders among patients with schizophrenia have helped identify health problems in this neglected category of patients who usually have shorter life span than non-schizophrenic patients [12,13]. A review of the literature failed to show studies carried out in the Arab world regarding the prevalence of metabolic disorders and its associated factors among patients with mental illness. Actually studies and published research in the field of mental health are few in the Arab world [14–16]. Published research in this area has concentrated mainly on medication adherence to antipsychotic medications [15,16]. Therefore, our study is one of the few in the Arab world in the field of health among patients with mental illness. For that reason, this study was carried out (1) to investigate the prevalence of pre-DM and DM among a sample of patients with schizophrenia, (2) to compare the results with those reported in the general population of Palestine, and (3) to determine significant associations with dysglycemia defined as having either pre-DM or DM.

2. Materials and methods

2.1. Study design

This is a cross sectional study conducted from August 2011 until February 2012 at governmental primary healthcare psychiatric centers in Northern West-Bank.

2.2. Study area and sample size

For this study, Nablus, Jenin, Tulkarm, and Qalqilai districts were selected. In Palestine, where the study took place, 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 United Nations Relief and Works Agency (UNRWA), health services belonging to national and international non-non-governmental organizations (NGOs) and some private health sector (for profit) organizations. In Palestine, mental health care services are primarily provided by the government, and by few non-governmental organizations. Several governmental psychiatric primary health care centers are located throughout Palestine. However, most of these centers are under-staffed and under-resourced [17].

All patients attending the abovementioned psychiatric healthcare centers during the study period with the following criteria were invited to participate: (1) age above 16 years old, (2) diagnosed with schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), (3) not suffering from an acute attack of illness during the past year, and (4) their drug regimen had not been changed in the last 6 months. A convenience, non-probability, sampling method was used. In order to estimate with sufficient precision the prevalence of pre-DM, we 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, a sample size of approximately 240 clients currently attending the governmental primary psychiatric healthcare centers in North West-Bank was needed.

2.3. Study tool: data collection form

Data collection form to cover all data items needed was developed. The form covered the following areas: socio-demographic variables, length of psychiatric illness; pharmacological treatment currently being used; history of psychiatric hospitalization, waist circumference, fasting blood glucose (FBG) measured in mg/dl and glycated hemoglobin (HbA1c). Focus group discussions were continuously held between the research team to maintain the integrity of the data collection process. Regular evaluations took place throughout the abstraction period to identify any problems in data collection, the interpretation of definitions, and the application of study criteria. Before commencing data analysis, an extensive series of checks were performed for data consistency, proper sequences of data, and an evaluation of missing or incomplete data. The data collection form was modified by the principal researchers and the modified version was reviewed by experts to ensure content and construct validity. Data from the pre-test evaluation were not included in the final analysis. Approval to perform the study was obtained from the Palestinian MOH and the college of Graduate Studies at An-Najah National University and Institutional Review Board (IRB).

2.4. Tested variables

(1) Pre-DM and DM: The definition of pre-DM and DM was based on WHO definition seen in Table 1.

(2) Waist circumference (WC): WC 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 (ATP III) guidelines for definition of metabolic syndrome [18,19].

(3) FBG and HbA1c: Blood samples were collected from all subjects between 8:00 and 9:00 (A.M.) after 12 h overnight fasting. Blood was collected from an ante-cubital vein punctures and was collected while subject or 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.

(4) 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.

| Table 1 – Definition of diabetics categories based on the World Health Organization. |
|-----------------------------------|----------------------------------------------------------------------------------|
| Diabetic category                | World Health Organization [48,49]                                               |
| Diabetic                          | F{}B{}G ≥7.0 mmol/l (126 mg/dl)                                                  |
|                                   | HbA1C <6.5%                                                                  |
| Pre-diabetic                      | F{}B{}G 6.1 to 6.9 mmol/l (110 mg/dl to 125 mg/dl)                               |
| Normal                            | F{}B{}G ≤6.1 mmol/l (110 mg/dl)                                                 |
| Abbreviation: FBG, fasting blood glucose. |                                                                                         |
(5) 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 [20,21]. Daily doses of antipsychotics, including depot antipsychotics, were converted to approximate chlorpromazine equivalents (CPZeq) using published guidelines [22,23]. 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. Total CPZeq dose was calculated by adding CPZeq for each antipsychotic drug in patient’s medical file.

2.5. 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.

2.6. 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 for all normally distributed continuous variables; while median and inter quartile range (Q1–Q3) was used for continuous variables that were not normally distributed. All statistical analyses were conducted using Statistical Package for Social Sciences SPSS (PASW version 18.0; IBM, Somers, NY) statistical packages for Windows. The conventional 5% significance level was used throughout the study. Comparison of the prevalence of pre-DM and DM between patients with schizophrenia with those in the general population was carried out using binomial chi square test. Variables were tested for normality using the Kolmogorov–Smirnov test. Statistical significance for inter-group differences was assessed by Student’s t-test for continuous variables. Univariate analysis and multiple logistic regression were used to find the significant predictors of dysglycemia among patients with schizophrenia. Correlation between FBG, HbA1c and insulin resistance among schizophrenic clients was tested by Pearson’s correlation coefficient.

3. Results

3.1. General descriptive statistics of the study sample

During the study period, 250 patients met the inclusion criteria; 68 (27.2%) were females and 182 (72.8%) were males. The mean age of the clients was 41.9 ± 11.8 [95% CI 40.5–43.4] 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).

Table 2 – General characteristics of the study sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) or median (Q1–Q3) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>182 (73.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (27.2%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.9 ± 11.8</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
</tr>
<tr>
<td>Less than 30</td>
<td>43 (17.2%)</td>
</tr>
<tr>
<td>30–40</td>
<td>76 (30.4%)</td>
</tr>
<tr>
<td>40–50</td>
<td>80 (32%)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>51 (20%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>105 (42%)</td>
</tr>
<tr>
<td>Village/camp</td>
<td>145 (58%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>School education less</td>
<td>213 (85.2%)</td>
</tr>
<tr>
<td>College education</td>
<td>37 (14.8%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>138 (55.2%)</td>
</tr>
<tr>
<td>Single/Divorced</td>
<td>112 (44.8%)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>153 (61.2%)</td>
</tr>
<tr>
<td>No</td>
<td>97 (38.8%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>219 (87.6%)</td>
</tr>
<tr>
<td>Working</td>
<td>31 (12.4%)</td>
</tr>
</tbody>
</table>
| Duration of psychiatric illness (years) | 15 (Q1–Q3:9–20)  
<10 years                     | 89 (35.6%)                           |
| >years                        | 161 (64.4%)                          |
| Number of psychiatric hospitalization | 1 (Q1–Q3:0–2) |

Abbreviations: Q1–Q3, lower quartile–upper quartile; SD, standard deviation.

The median duration of illness was 15 (Q1–Q3:9–20) years. The median number of psychiatric hospitalization of the clients during their lifetime was 1 (Q1–Q3:0–2). Based on normal values for WC, 56 (82.4%) female patients had WC above the normal value while only 58 (31.9%) male patients had a WC above the normal value. Abdominal obesity was significantly associated with being female (P < 0.01). Basic demographic and clinical characteristics of the clients are shown in Table 2.

3.2. Prevalence of pre-diabetes and diabetes mellitus in the study sample

The mean FBG of the study sample was 99.5 ± 47.5 mg/dl (95% CI 93.5–105.4) while that of the HbA1c value was 5.6 ± 1.1% (95% CI 5.5–5.7). There was a significant positive correlation between FBG and HbA1c (r = 0.22; P < 0.01). Based on WHO criteria, 27 patients (10.8%) had a FBG >126 mg/dl (diabetes) while 34 (13.6%) patients had FBG between 110 and 125 mg/dl (pre-diabetes) (Table 3). For the comparison of the prevalence of pre-diabetes in patients with schizophrenia and general population, we used the WHO criteria because previously published studies about pre-DM and DM in Palestine had used the WHO criteria. The prevalence of pre-DM but not that of DM in the study sample was significantly higher than that reported in the general population of Palestine (Table 4).
3.3. Factors associated with dysglycemia

Among the study sample, 189 (75.6%) were considered to have euglycemia and 61 (24.4%) have dysglycemia. Levels of FBG and HbA1c for patients with dysglycemia and euglycemia are shown in Table 5. Univariate analysis showed that the following variables were significantly associated with dysglycemia: female gender, advanced age, abnormal WC, longer duration of the illness, use of depot antipsychotics, use of anticholinergic medications, use of antipsychotic drug combinations, and use of high CPZeq.

All variables that had significant associations with dysglycemia in univariate analysis were entered into multiple logistic regressions to determine significant predictors of dysglycemia among schizophrenic clients (Table 6). The results of multiple logistic regression showed that only advancing age and abnormal waist circumference were significant predictors of dysglycemia among clients with schizophrenia.

4. 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 with the general population of Palestine [24-26]. Because our study is a cross-sectional study, we were unable to investigate a possible causal relationship between the increased rates of pre-DM and antipsychotic treatment. Furthermore, as some patients had been treated with more than one antipsychotic during their entire illness period, we could not calculate the prevalence of pre-DM and DM for individual antipsychotics. 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 [7]. 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 [27].

Data regarding the prevalence of DM in our study are similar to earlier reports, including the 13% prevalence of DM found in the CATIE study [28] and other studies reported in American and European patients with schizophrenia [6,7,29,30]. The prevalence of DM reported in our study was higher than that reported in Taiwanese schizophrenia study (7.9%) [31] and a study in France (2.2%) [32].

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 diabetes, hypertension and dyslipidemia commonly coexist [6]. Therefore it seems likely that people with dysglycemia may also have comorbidities that further increase their risk of cardiovascular disease and premature death [33]. Early detection of pre-DM and effective education about healthy living should help to reduce the risk of patients developing DM and its complications, and may ultimately help to improve long-term outcomes.

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. Our study indicated that the following variables were significantly associated with dysglycemia: female gender, advancing age, abdominal obesity (abnormal WC), duration of psychiatric illness, use of depot medications, use of anticholinergic medications, use of antipsychotic drug combinations, and use of higher dose of antipsychotic agents measured in CPZeq. However, only advancing age and abnormal abdominal obesity were significant predictors of dysglycemia in schizophrenic patients. The current literature does not provide a clear understanding of which risk factors best predict the development of dysglycemia in patients with schizophrenia.

Our study suggested that female gender was significantly associated with increased risk for dysglycemia but was not a significant predictor of dysglycemia. This finding is consistent with a previous report of increased prevalence of DM among women treated with first generation typical antipsychotic drugs [7]. However, another study has not found gender as a risk factor for antipsychotic-associated DM [34]. The exact reason for the higher risk of DM in female schizophrenia cannot be determined in view of the current cross sectional study. 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 DM [35].

In our study, age was a significant risk factor and predictor for dysglycemia which is similar to that reported in other studies [7,32,33]. 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. 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 [36,37]. Another risk factor that was found to be a significant predictor of dysglycemia was abnormal WC. 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 the 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 the presence of schizophrenia itself, may be associated with increased intra-abdominal fat stores [38,39]. Other studies reported similar findings regarding an association of obesity and DM in schizophrenic clients [40,41]. 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 no significant association between family history of DM and dysglycemia. This is in contrast to results reported by other researchers [34,41]. Furthermore, our data showed no significant association with the type of antipsychotic (FGA versus SGA) in contrast to other reported studies [42]. This discrepancy, however, could be explained in terms of the population characteristics – longer duration of illness, the cumulative effects of both first and second-generation antipsychotic drugs 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

Table 6 – Multilogistic regression for variables significantly associated with dysglycemia among patients with schizophrenia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P value</th>
<th>Odds ratio with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>-0.64</td>
<td>0.108</td>
<td>0.53 (0.24–1.15)</td>
</tr>
<tr>
<td>Higher age</td>
<td>0.05</td>
<td>0.003</td>
<td>1.06 (1.02–1.10)</td>
</tr>
<tr>
<td>Abnormal WC</td>
<td>0.94</td>
<td>0.013</td>
<td>2.56 (1.21–5.38)</td>
</tr>
<tr>
<td>Duration of psychiatric illness &lt; 10 years</td>
<td>0.11</td>
<td>0.810</td>
<td>1.12 (0.45–2.77)</td>
</tr>
<tr>
<td>Use of depot antipsychotic agents</td>
<td>0.19</td>
<td>0.627</td>
<td>1.21 (0.56–2.59)</td>
</tr>
<tr>
<td>Use of anticholinergic agents</td>
<td>0.67</td>
<td>0.132</td>
<td>1.95 (0.82–4.67)</td>
</tr>
<tr>
<td>Use of monotherapy</td>
<td>0.27</td>
<td>0.558</td>
<td>1.30 (0.54–3.17)</td>
</tr>
<tr>
<td>Total CPZeq &lt; 600 mg</td>
<td>0.05</td>
<td>0.363</td>
<td>1.01 (0.99–1.02)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; β, coefficient of predictor variables; CPZeq, chlorpromazine dose equivalencies; WC, waist circumferences.
originally thought [43]. Furthermore, the smaller sample size of patients using SGA in our study might be the reason for not detecting a difference. A meta-analytic review suggested that the association between atypical antipsychotics and diabetes risk remains controversial because of the poor methodological quality in most studies [44,45]. 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) [46]. 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 reasonable.

4.1. Limitations of the study

Our analyses had a number of limitations. First, the cross-sectional nature of this study limits the ability to establish a temporal relationship between exposure to the development of DM. In addition, there is a possibility for bias in examining drug exposure because a drug may have been administered after DM was diagnosed. Second, the sample size that we enrolled was small which may have limited our ability to detect other statistically significant risk factors associated with DM. Third, the medical chart data may have been inaccurate or incomplete, and there may have been misclassification in the identification of diabetes. The prevalence of diabetes may be underestimated because of under-recognition of diabetes among patient with schizophrenia [47].

5. Conclusion

This study confirmed the high prevalence of dysglycemia among patients diagnosed with schizophrenia, supporting the need for enhanced monitoring in this population. Risk factors for dysglycemia in this sample identified by the logistic regression analysis included older age and abnormal waist circumference.

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 waist circumference and take into consideration age of the patient.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES


