Risk Factors of Metabolic Syndrome among Egyptian Patients with Schizophrenia

Hatata H[1], El-Gohary G[2], Abd-Elsalam M[2], Elokda E[3]

[1]Department of Psychiatry, Ain Shams University, Cairo, Egypt.
[2]Department of Internal Medicine and Hematology, Ain Shams University, Cairo, Egypt
[3]Department of Community and occupational Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: The metabolic syndrome (MS) is a cluster of the most dangerous known cardiac risk factors (diabetes and pre-diabetes, abdominal obesity, high cholesterol level, and high blood pressure "BP". There is high mortality risk among people with mental illness due to physical health factors. Poor diet, lack of exercise, negative symptoms, stress, smoking, and abnormalities in the hypothalamic–pituitary–adrenal axis (HPA) has all been proposed as precursors to the link. **Objective:** to determine the risk factors of metabolic syndrome in a sample of Egyptian patients with schizophrenia. **Subjects and methods:** Sixty three patients were screened for metabolic syndrome using the IDF. Twenty four patients (38.09%) met the criteria for MS. **Results:** Increased waist circumference, higher body mass index, raised triglycerides level, increased blood sugar level, older age, emerged as significant predictors of metabolic syndrome in the sample. 39 (61.91%) patients did not meet the full criteria for the syndrome; however, 31 out of these 39 patients (49.2%) had 1-2 criterion of the syndrome. **Conclusion:** This study supports the systematic screening for metabolic syndrome in patients receiving antipsychotic drugs. Intervention programs which screen for and address the modifiable risk factors of metabolic syndrome is recommended.

Key words: Metabolic Syndrome, Schizophrenia, Egypt

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INTRODUCTION

Schizophrenia is associated with approximately 20% reduced life expectancy and the mortality rate from coronary heart disease is significantly higher compared to the general population[1]. The main risk factors for this higher rate of mortality are impaired glucose regulation/insulin resistance, obesity, dyslipidemia, and hypertension, which collectively constitute the cluster of interrelated disorders termed “metabolic syndrome” (MS). The high prevalence of MS in schizophrenic patients has assumed greater significance since the increase in the use of second-generation antipsychotics (SGAs) in the 1990s. Most of these SGAs have been associated with substantial weight gain, which is a major risk factor for diabetes and coronary heart disease[2].

Recently, most studies of the prevalence rates of MS in people with mental illness

have shown increased rates in comparison with those of the general population. Medication type and dose have been associated with differences in MS prevalence rates among patients with psychiatric illness[3].

Clozapine and Olanzapine, atypical antipsychotics, have been shown to be associated with weight gain[4] and diabetes mellitus[5] Clozapine has demonstrated its efficacy in the management of treatment-resistant schizophrenia but is also associated with deleterious effects on a range of metabolic parameters, such as weight gain, hypertriglyceridemia, increased total cholesterol level, and hypertension[6]. However, the risks of weight gain and developing diabetes mellitus are significantly lower with Risperidone compared to Olanzapine and Clozapine[4]. Therefore, Risperidone seems to be relatively safe with a low risk of metabolic side effects in chronic schizophrenia[7].

The mounting indications of an association between antipsychotics prescription and high MS risk provide further challenges to psychiatric prescribers who seek to balance risk and benefit in their decision to commence or continue treatment-resistant schizophrenia. In a survey of 300 randomly selected psychiatrists in the United States in 2003, 43%-48% were willing to risk metabolic side effects in lieu of the therapeutic benefits of the atypical antipsychotics[8].

Understanding the prevalence and predictors of MS among patients taking antipsychotic drugs may enhance prescribers' abilities to make more considered risk–benefit decisions. Nasrallah suggests that as clinicians refine their practice around the use of the atypical antipsychotics, more research, resources, and knowledge will be required to enable clinicians to fully understand the risk–benefit considerations they face when prescribing atypical antipsychotics[9].

The purpose of this study is to determine the risk factors of MS in a sample of Egyptian patients with schizophrenia.

SUBJECTS AND METHODS

Subjects were collected from one governmental hospital (Institute of Psychiatry, Ain Shams University), and one private hospital (Psychological Medicine Hospital "Adel Sadek Hospital"). Hence, increasing the representativeness of the sample with regard to demographic variables including different socioeconomic status. Data was collected between June and September 2008. Subjects with a primary diagnosis of schizophrenia or schizoaffective disorder using DSM-IV criteria were approached and asked to consent to be screened for MS using the IDF (2007) criteria.

Measures:

Diagnoses were based on a Structured Clinical Interview with resultant DSM-IV diagnosis (SCID- I)[10]. Also a screening sheet developed by the author including age, disease duration, marital status, occupation, past and family history of medical illnesses (Diabetes, cardiovascular diseases, Hypertension and liver disease), special habits including smoking, eating habits and exercise. Gestational diabetes, polycystic ovarian syndrome, and smoking status variables were also collected. The sociodemographic questionnaire[11] was applied as well.

The IDF diagnostic criteria include waist circumference ≥94cm for men and ≥80cm

for women, with ethnicity-based values, plus any two of the following: raised triglyceride (TG) level (≥150mg/dl or ≥1.7mmol/L) or specific treatment of this abnormality, reduced high-density lipoprotein (HDL) cholesterol (≤40mg/dl or ≤1.03mmol/L in men and ≤50mg/dl or ≤1.29mmol/L in women) or specific treatment of this abnormality, raised systolic BP (≥130) or diastolic BP (≥85mmHg) or treatment of previously diagnosed hypertension, and raised fasting plasma glucose (FPG) level (≥100mg/dl or ≥5.6mmol/L) or previously diagnosed type 2 diabetes.

Laboratory investigations were collected by the ward nurse, under supervision of the first author. Samples for fasting blood sugar and full lipid profile were collected after 6 hours overnight fasting and 12 hours overnight fasting, on separate days, respectively. All the analyses of samples were completed by Ain Shams University Psychiatry Hospital laboratory. Waist circumference, body weight and BMI were assessed by the first author. Insulin resistance was assessed indirectly by the TG/HDL ratio marker, with a ratio of ≥3.5 being significant[12]. Ethics approval was granted by the Ethical Committee Human Research of Ain Shams University School of Medicine.

Statistical analysis:

Statistical analysis of data was done by IBM computer using SPSS (statistical program for social science version 12) as follows: Description of quantitative variables as mean, SD and range. Description of qualitative variables as number and percentage Unpaired t-test was used to compare two groups as regard quantitative variable in parametric data (SD<50% mean). Mann Whitney Willcoxon test was used instead of unpaired t-test in non parametric data (SD>50% mean). Multivariate analysis (logistic regression) was performed to find out the most important independent predictors of cretin outcome, using forward condition technique. P>0.05 insignificant, P<0.05 significant, P<0.01 highly significant[13].

RESULTS

The study was conducted on 63 patients 49 males and 14 females. The demographic data of the patients are shown in tables (1 and 2). All patients met DSM-IV criteria for schizophrenia. 30 patients had paranoid schizophrenia, 13 had schizoaffective schizophrenia, 16 had undifferentiated schizophrenia, 3 had disorganized schizophrenia and 1 was catatonic.

Table 1 shows that MS was more prevalent among paranoid cases, employed and a longer duration of drug intake especially Risperidone, with higher BMI and waist circumference compared to negative group with statistically significant difference in between by using either t-test or chi-square test.

Table 2 shows that positive cases had older age, a longer duration of drug intake, higher BMI and waist circumference compared to negative group with statistically significant difference in between by using either Mann Whitney test. On the other hand there is no significant difference between both groups as regard other variables.

According to the IDF criteria for diagnosis of metabolic syndrome[14]: 24 (38.09%) patients met the criteria for the syndrome (3 or more MS criteria). 39 (61.91%) patients did not meet the full criteria for the syndrome (2 or less MS criteria); however,

31 out of these 39 patients (49.2%) had 1-2 criterion of the syndrome (table 3-4). Table (3) shows that positive cases had higher level of cholesterol and LDL , with low HDL level compared to negative cases with highly statistically significant difference in between by using unpaired t-test. Table 4 shows that positive cases had higher level of cholesterol LDL, TG, TG/HDL and FBS with low HDL level compared to negative cases with highly statistically significant difference in between by using unpaired t-test.

Higher body mass index, waist circumference, raised triglycerides level, increased blood sugar level, and duration of drug intake emerged as significant predictors of metabolic syndrome in the sample. Table 5 shows that TG above 150, age above 35 and BMI above 29 with FBS above 110 are considered the most important independent predictors of MS. By using logistic regression forward condition technique.

Insulin resistance was assessed indirectly by the TG/HDL ratio marker, with a ratio of ≥3.5 being significant[15]. All the male patients with or without metabolic syndrome full criteria have an elevated ratio. On the other hand, all female patients with or without MS showed a normal ratio.

Moreover, the incidence of metabolic syndrome among male subjects was found to have statistical significance according to the type and duration of treatment. In the present study, MS was more prevalent in patients with longer duration of drug intake especially Risperidone. There was a near equal incidence between both Olanzepine and Clozapine. Haloperidol was the lowest in the incidence of occurrence of MS. Table 6 shows that cases treated by risperidone had the highest BMI compared to other drugs with significant difference in between by using one way ANOVA test.

Interestingly, BMI was higher in patients on Risperidone, confirming that Risperidone has significant relation with MS. However, in female patients, the type of treatment showed no statistical significance. Yet, older age (>35) as a predictor, showed significant values in females only.

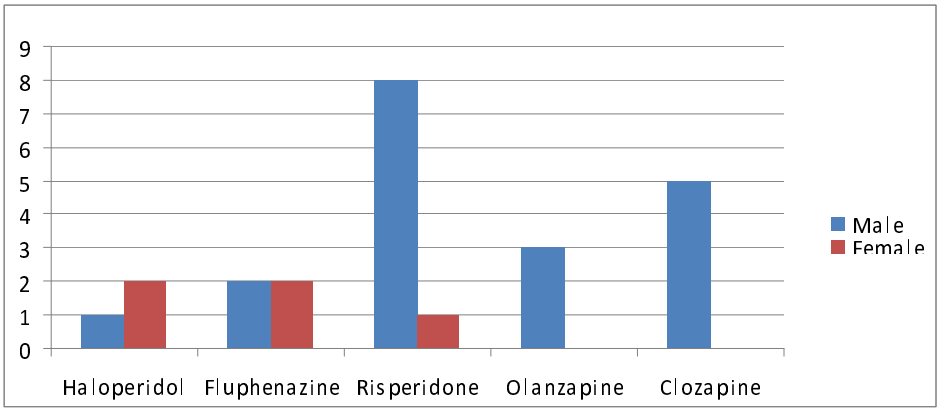

Figure (1) Number of patients fulfilling criteria for MS in comparison to type of antipsychotics

Table (1) Comparison between both studied groups as regard general data among males

Variables		MS Yes	MS No	P
Age	years (Mean±SD)	34±8	31±8	>0.05
Disease duration	years (Mean±SD)	10.8±6	7±5	>0.05
BMI		30±5	24±4	**<0.01 HS**
Waist circumference	cm	106±10	87±12	**<0.01 HS**
Duration drug intake	weeks (Mean±SD)	11.1±6	6.8±4	**<0.05 S**
Duration of smoking	years (Mean±SD)	10.9±6	8.6±4	>0.05
Social class	Very low Low Moderate High	8(42.1%) 2(10.5%) 3(15.8%) 6(31.6%)	5(16.7%) 7(23.3%) 6(20%) 12(40%)	>0.05
Smoking	No°	12(63.2%)	22(73.3%)	>0.05
Marital status	Single Married Divorced	13(86.7%) 2(13.3%) 1(5.3%)	15(100%) 0 1(3.3%)	>0.05
Diagnosis	Paranoid Undifferentiated Schizoaffective Hebephrenic Catatonic	12(63.2%) 3(15.8%) 4(21.1%) 0 0	11(36.7%) 9(30%) 7(23.3%) 2(6.7%) 1(3.3%)	**<0.05 S**
Occupation	Employed Unemployed	9(47.4%) 10(52.6%)	7(23.3%) 23(76.7%)	**<0.05 S**
Exercise	No°	2(10.5%)	3(10%)	>0.05
Medications	Haloperidol Fluphenazine Risperidone Olanzepine Clozapine	1(5.3% 2(10.5%) **8(42.1%)** 3(15.8%) 5(26.3%)	8(26.7%) 4(13.3%) 7(23.3%) 5(16.7%) 6(20%)	**<0.05 S**

Table (2) Comparison between both groups as regard general data among females

Variables		MS Yes	MS No	P
Age	years (Mean±SD)	41±8	34±11	**<0.05 S**
Disease duration	years (Mean±SD)	7.4±4	8±3.8	>0.05
BMI		32±7.5	27±4	**<0.05 S**
Waist circumference	cm	107±12	73±25	**<0.05 S**
Duration of drug intake	weeks (Mean±SD)	9.5±4	5.2±1.7	**<0.05 S**
Social class	Very low Low Moderate High	1(20%) 1(20%) 1(20%) 2(40%)	3(33.3%) 0 4(44.4%) 2(22.2%)	>0.05
Marital status	Single Married Divorced	2(40%) 1(20%) 2(40%)	6(66.7%) 2(22.2%) 1(11.1%)	>0.05
Diagnosis	Paranoid Undifferentiated Schizoaffective Hebephrenic	3(60%) 2(40%) 0 0	4(44.4%) 2(22.2%) 2(22.2%) 1(11.1%)	>0.05
aOccupnoit	Employed Unemployed	1(20%) 4(80%)	3(33.3%) 6(66.7%)	>0.05
Medications	Haloperidol Fluphenazine Risperidone Olanzepine Clozapine	2(40%) 2(40%) 1(20%) 0 0	1(11.1%) 3(33.3%) 1(11.1%) 3(33.3%) 1(11.1%)	>0.05 NS

Table (3) Comparison between both groups as regard laboratory data among males

Variables	MS Yes	No	P
Cholesterol (mg/dl)	245±88	228±93	>0.05
TG (mg/dl)	302±169	165±41	**<0.01 HS**
HDL (mg/dl)	39.7±8	47±10	**<0.01 HS**
TG/HDL (mg/dl)	**8.1±5**	3.6±2	**<0.01 HS**
LDL (mg/dl)	144±87	144±81	>0.05#
FBS (mg/dl)	99±15	89±10	>0.05

Table (4) Comparison between both groups as regard laboratory data among females

Variables	MS Yes	No	P
Cholesterol (mg/dl)	226±47	200±59	>0.05
TG (mg/dl)	154±56	97±35	**<0.05 S**
HDL (mg/dl)	50±4	58±8	**<0.05 S**
TG/HDL (mg/dl)	3±1	1.6±0.6	**<0.01 HS**
LDL (mg/dl)	143±47	121±52	**<0.05 S**
FBS (mg/dl)	119±25	89±11	**<0.01 HS**

Table (5) Relation between different risk factors and MS among the studied cases:

Variables	Beta co-efficient	P	Odd's (95% CI)
TG >150 mg/dl	-1.8	**<0.05 S**	1.9(1-6)
Age >35 years	-1.9	**<0.05 S**	1.2(1-4)
BMI >29	-2.3	**<0.05 S**	2.6(1-12)
FBS>110mg/dl	-3	**<0.05 S**	0.7(0.2-5)

Table (6) Relation between BMI & different medications among males and females:

Variables	Males	Females
Haloperidol	24±4	26.3±1
Fluphenazine	25±4	25.6±7
Risperidone	**30±6**	**32.5±14**
Olanzepine	27.8±4	37±5
Clozapine	27±5	-
P value	**<0.05 S**	**<0.05 S**

DISCUSSION

Most studies all over the world of the prevalence rates of MS in people with mental illness have shown increased rates in comparison with those of the general population[3]. In recent years, especially after the introduction of new generation antipsychotics, researchers have frequently discussed the effect of new generation antipsychotics on metabolic problems seen in patients with schizophrenia. In a study of 689 patients with schizophrenia, identified prevalence rates of 40.9% and 42.7% using the NCEP (National Cholesterol Education Program) definition and the American

Heart Association definitions of MS, respectively[15-17]. In a Finnish study of 8,028 patients, the authors obtained a prevalence rate of 36.2% for people with schizophrenia, 41.4% for other non affective psychosis, 25% for affective psychosis, and 30.1% for people without psychotic disorders[18].

The use of the new generation of antipsychotics was the one to blame in these debates although they have proven to be more effective in treatment of relapsing and resistant cases. What enforces this believe is the presence of some studies on naive patients which reveal no difference in the incidence of MS between them and the normal population. Also the first episode psychotic patients having a schizophrenia spectrum disorder do not differ from healthy controls, in their baseline measures of glucose and lipid metabolites, nor in the prevalence of diabetes or its precursors, before (or close to) the onset of antipsychotic treatment[19]. However, most patients with psychotic disorders are currently treated with novel antipsychotic medications which are associated with varying, and some with alarming, magnitude of weight gain[2].

Another independent study, conducted with a Chinese Han population, reported that there were no differences in fasting plasma levels of glucose, insulin, and lipid profile between drug-naïve first-episode schizophrenia patients and healthy controls (46 patients and 38 controls in each group)[20]. There was no report of glucose tolerance in this study.

In our study, 24 (38.09%) patients met the criteria for the syndrome (3 or more MS criteria). 39 (61.91%) patients did not meet the full criteria for the syndrome (2 or less MS criteria); however, 31 out of these 39 patients (49.2%) still had 1-2 criterion of the syndrome.

Consistent with our results that risperidone has significant relation with the development of MS, in addition patients on Risperidone monotherapy had significantly impaired body fat percentage, BMI, triglyceride and HDL-cholesterol compared to healthy volunteers[21]. Although their study has limitations, such as lack of comparison with other antipsychotics, chronic Risperidone treatment may cause such metabolic abnormalities. Also, a retrospective chart review reported that Risperidone-treated patients had significant increases in weight, BMI and fasting triglyceride at 1 year of treatment compared with the baseline[22]. On the other hand, the risk of weight gain, diabetes and Hyperlipidemia in patients treated with Risperidone is lower than in those treated with Clozapine and Olanzapine[23]. However, a possible increase in risk would be predicted to occur in association with any second-generation antipsychotic that increases weight and adiposity. Therefore, regular metabolic monitoring is required during Risperidone treatment.

In the present study, we found that Clozapine and Olanzapine have no significant relation to MS. However, we cannot neglect the possibility that this may be attributed to small sample size on these medications. Especially many previous studies have shown the opposite[24].

In a study of 93 patients attending a Clozapine clinic in the United States showed that the prevalence of MS in the study group to be 53.8% (NCEP definition)[25]. In addition, another study of 1,691 psychiatric inpatients in North America, found that 69.3% had at least one correlate of MS[26]. In this study, the odds of

a patient having one or more MS correlates were 8 times greater among patients receiving Clozapine compared with those receiving other antipsychotics.

In a previous longitudinal study, the first episode psychotic patients showed an average weight gain of 10.2kg and an increase in total and LDL cholesterol as early as 3–4 months after treatment with Olanzapine[27]. Similarly, a study with the Chinese population reported that after 10 weeks of treatment with either risperidone or chlorpromazine, significant increase in fasting total and LDL-cholesterol, triglycerides and glucose, as well as subcutaneous and intra-abdominal fat, was observed[20]. Excessive weight gain, abdominal obesity, and dyslipidemia are risk factors for type 2 diabetes and hypertension, which could account for the higher prevalence observed in the (Clinical Antipsychotic Trials of Intervention Effectiveness) CATIE study. These observations underscore the importance of regular monitoring in patients treated for psychotic disorders, for onset of pre-diabetes and dyslipidemia, as has been previously suggested[28]. In addition, it may be particularly important to incorporate behavioral and/or pharmacological interventions when patients are treated with SGAs[29].

On the other hand, in our study other risk factors were also identified. Age >35 years, BMI >29, TG >150 mg/dl and FBS >110mg/dl can be used as predictors for MS in our Schizophrenic patients.

This is consistent with a Swedish study of 269 patients, MS prevalence (NCEP) was 34.6% and highest within the age group of 40 to 49 year-olds (43%). Patients who were prescribed Clozapine had the highest prevalence rate of 48.5%[30]. BMI >28.7 is a significant predictor of MS with highest accuracy in terms of specificity and sensitivity[31].

Although attempts at determining prevalence rates of MS need to continue among patients, the predictors of the syndrome are all known to be modifiable risk factors. Several recent publications provide frameworks for the management of metabolic considerations in the context of antipsychotic medication prescription[32]. Attempts have been made at modifying the components of MS among clozapine patients, predominantly with diet and exercise interventions[24], pharmacological approaches and increase of patient's knowledge of MS[33]. These studies are, however, limited in size, and further controlled trials need to be conducted to establish their efficacy.

Several studies have suggested that behavioral/educational interventions alone[34] or in conjunction with medication management[35] may be effective in controlling weight gain associated with antipsychotic treatment.

A key concern for many clinicians is that increasing patient knowledge of the relationship between MS and their prescribed antipsychotic may affect an increase in antipsychotic medication non adherence. Discontinuation rates of antipsychotics have been attributed to side effects such as weight gain[36]; however, the ethical and medicolegal issues encountered as a consequence of not fully informing the patient of these side effects are likely to be detrimental to individual clinicians. There is debate over who is responsible for monitoring MS. Points of view differ as to whether responsibility should lie with primary or secondary care services. A survey of psychiatrists in the United

Kingdom[8] found that 56% of respondents agreed that primary care services should take full responsibility for physical health monitoring. Although there needs to be a coordinated approach, primary responsibility should rest with the treating mental health team. As the course and treatment of mental illness may increase the risk of physical health abnormalities, it would make sense that the treating mental health team takes responsibility for coordinating this aspect of care. Localized service protocols for systematic screening for MS, sharing and interpretation of results, and provision of treatment should be led by mental health services with the collaboration of primary care general practitioners and specialist medical services[37].

Our study was subject to certain limitations. First, it is a Cross sectional study and there is an obvious need in the literature for more studies using a prospective or longitudinal design in order to explore the long term effect of antipsychotic on schizophrenic patients. Second; all the subjects included were inpatients. Third, small sample size. Fourth, most of the subjects are males. Fifth, some antipsychotics were not included as Aripiprazole. Ziprasidone, Qutiepine and Sertindole.

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Address of Correspondence:

Hatata H. *Lecturer of Psychiatry, Ain Shams University, Cairo, Egypt.*
e-mail: *drhatata@yahoo.com*