# Metabolic syndrome and serum level of adiponectin in Egyptian patients with schizophrenia

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**Abstract**

Metabolic syndrome is an important risk factor for cardiovascular morbidity and mortality in schizophrenic patients. In Egypt, however, its prevalence among these patients is uncertain. Also, little is known about the relationship between the metabolic syndrome and serum level of a substance such as adiponectin among Egyptian patients with schizophrenia, at a time when in other nations the usefulness of adiponectin for the prediction of insulin resistance and metabolic syndrome is attracting much attention.To assess the frequency of metabolic syndrome and the serum level of adiponectin in a sample of Egyptian outpatients with schizophrenia, testing the hypotheses that (a) the prevalence of the metabolic syndrome is higher among schizophrenic patients compared with a normal group of subjects, and (b) serum adiponectin level has an inverse relationship with the parameters of the metabolic syndrome in these patients. 50 consecutive out-patients with schizophrenia, classified into early illness (N= 26 patients) and chronic illness (N= 24 patients) groups, and a matched group of 100 apparently healthy controls were compared using the International Diabetes Federation (IDF) criteria and serum levels of adiponectin. 19 patients (28%) as opposed to five controls (5%) met the criteria of the metabolic syndrome. None of these patients or controls, however, was previously diagnosed or treated for this syndrome or for any of its components. Serum adiponectin level in the patients group was negatively associated with all the parameters of the metabolic syndrome except the HDL level with which it was positively associated. In the control group, however, there were no such significant correlations. Patients, classified by the type of antipsychotics, did not differ in the serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters. The metabolic syndrome is highly prevalent among treated Egyptian patients with schizophrenia. Thus, assessment of the presence and monitoring of the associated risks of the metabolic syndrome should be part of the clinical management of such patients. In line with the mounting body of evidence in other populations, this study indicates that measurement of serum adiponectin level by ELISA technique may be a useful biomarker for the metabolic syndrome in schizophrenic patients.

## Introduction

There is an excess of death from natural causes among people with schizophrenia (Joukamaa et al., 2006; Mitchell and Malone, 2006) primarily due to cardiovascular disorders (Davidson, 2002; Van Gaal, 2006). One major risk factor for these disorders is the metabolic syndrome (Chen et al., 2006) which is reported to have a higher frequency among schizophrenic patients (De Hert et al., 2006; Heiskanen et al., 2003) and is receiving significant attention because of its high prevalence in the general population (approximately 24% in the United States) (Ford et al., 2002) and its role as an independent risk factor for cardiovascular

morbidity and mortality (comparable to smoking) (Lamarche and St-Pierre, 2005; Tonstad and Svendsen, 2005). The syndrome was originally identified by Reaven (1988; 1992) as syndrome X or the insulin resistance syndrome for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides and low HDL concentration, and has been given several other names, including the 'plurimetabolic syndrome', and the 'deadly quartet' (Kaplan, 1996). Associated with a 3 fold and 2 fold increase in type 2 diabetes and cardiovascular disease (CVD), respectively, it is thought to be a driver of the modern day epidemics of diabetes and CVD and has become a major public health challenge around the world (Zimmet et al., 2005). In 1998, WHO proposed a definition for the syndrome and chose to call it the 'metabolic syndrome' (Alberti and Zimmet, 1998). This name was chosen primarily because it was the cause of all the components of the syndrome. Since its initial description, several definitions of the syndrome have emerged. Each of these definitions used differing sets of criteria, which reflected contrasting views on pathogenic mechanisms and the need for clinical usefulness, e.g., the modification version of the WHO definition introduced by the European Group for study of Insulin resistance (EGIR) (Balkau and Charles, 1999) and the ATP-III definition introduced by the National Cholesterol Education Program (NCEP) of USA (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002). The use of these definitions to conduct research into the metabolic syndrome in diverse populations resulted in wide ranging prevalence rates, inconsistencies and confusion, and spurred on the vigorous debate regarding how the metabolic syndrome should be defined. In response to this controversy, the International Diabetes Federation (IDF) has recently proposed a new definition (Alberti et al., 2005), which is convenient to use in clinical practice and is applicable to populations around the world so that data from different countries can be compared (Alberti et al., 2006; Zimmet et al., 2005).

The mechanisms underlying the metabolic syndrome are not fully known, but thought to be multiple: among them, the adipose tissue excess is suspected to play a major role (Fasshauer and Paschke, 2003; Flier, 2001). Adipose tissue, in addition to its function as an energy storage depot, has been increasingly recognized as an important endocrine organ that secretes a large number of biologically active hormone-like peptides, named adipokines (Ahima, 2006). Among them are mainly leptin and TNF-α as pathogenic factors and adiponectin, also known as ACRP-30 (Scherer et al., 1995), Adipo-Q (Hu et al., 1996), apM1 (Maeda et al., 1996), or GBP28 (Nakano et al., 1996), as a protective factor (Moller and Kaufman, 2005). Experimental studies in mice have shown that intraperitoneal administration of adiponectin lowers plasma glucose (Combs et al., 2001). In humans, decreased plasma adiponectin levels have been demonstrated in patients with obesity and diabetes (Arita et al., 1999; Mannucci et al., 2003). Obesity is associated with the changes in the production of adipokines consisting of decreasing production of adiponectin and increasing production of leptin and TNF-α, which step by step deteriorate the metabolic status (Lee and Pratley, 2005).

In Egypt, some of the basic components of the metabolic syndrome, e.g., diabetes

mellitus and obesity, have become a focus of clinical attention in recent years. Diabetes, which was described for the first time in human history in Egypt (~1500 BC) has now become one of its major and emerging clinical and public health problem (Herman et al., 1995; 1998). By the year 2025, Egypt is expected to be among the top ten countries that have the highest prevalence rates of diabetes in the world, notably Type 2 diabetes (King et al., 1998). Obesity too, which was described in several members of the Ptolemys, the royal family that ruled Egypt from 305 to 30 BC (Michalopoulos et al., 2003), has now increased dramatically, particularly among Egyptian women (Galal, 2002) and is becoming a problem among Egyptian youth (Salazar-Martinez et al., 2006). Obesity and diabetes are also imposing major psychiatric challenges in Egypt (Abo Elwafa, 2002; El-Atrouni et al., 1992), and have become a subject of growing concern, at least because of the worldwide publicity regarding reported potential risk of the drug induced weight gain (e.g., Ananth et al., 2004; McIntyre et al., 2003; Ruetsch et al., 2005; Sharpe and Hills, 2003) and the diabetogenic effect of novel antipsychotics (e.g., Cohen et al., $2006_a$; Ramaswamy et al., 2006; Schwenkreis and Assion, 2004). Yet, the prevalence of the metabolic syndrome among schizophrenic patients is uncertain. Also, little is known about the relationship between serum level of a substance such as adiponectin and the metabolic syndrome among Egyptian patients with schizophrenia, at a time when in other nations the usefulness of adiponectin for the prediction of insulin resistance and metabolic syndrome is attracting much attention (Gilardini et al., 2006; Hara et al., 2006; Ogawa et al., 2005; Santaniemi et al., 2006; Tajtakova et al., 2006; Trujillo et al., 2005). The objective of this study, therefore, was to assess the prevalence of metabolic syndrome and the serum level of adiponectin in a sample of Egyptian outpatients with schizophrenia, testing the hypotheses that (a) the prevalence of the metabolic syndrome is higher among schizophrenic patients compared with a normal group of subjects, and (b) serum adiponectin level has an inverse relationship with the parameters of the metabolic syndrome in these patients.

## Method

### Participants

**Patients:** A total of 50 patients were recruited from consecutive attenders of the psychiatric out-patients clinic, Zagazig University Hospitals, Zagazig, Egypt, from July 2005 to June 2006, with a diagnosis of schizophrenia (F.20 of the ICD10) aged 18 to 60 years, for whom a stable regimen of antipsychotic medication was consistently prescribed for at least 3 months prior to recruitment. These patients had no history of chronic medical illnesses and were taking no medications, other than their antipsychotics, suspected to affect glucose or lipid metabolism. Other exclusion criteria included patients who were pregnant, active substance abusers, and those who were judged not to have the capacity to give consent.

Recruited patients were classified into two groups, the early illness group, which included patients below the age of 30 with less than 5 years' total duration of illness (N= 26), and the chronic illness group which included those above 30, with more than 10 years' duration of illness (N= 24). Patients were also classified by the type of antipsychotic as on typical (N= 15), atypical (N= 21) and mixed (N= 14).

**Controls:** 100 matched subjects who had no history of treatment for any neuropsychiatric disorder, were selected from apparently healthy hospital staff and companions of patients admitted for minor surgery, at the same hospitals, Zagazig, Egypt.

Informed consent was obtained from all participants after the procedures had been fully explained.

**Assessments**

**Clinical Assessments:**

Patients were subjected to a semi-structured psychiatric interview during which the ICD-10 diagnosis of schizophrenia was confirmed and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was applied. Data evaluated from all patients and controls included a standardized medical history and a thorough physical examination. Waist circumference was measured at the level of the umbilicus, at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was computed as the mean of two measurements in the sitting position recorded, with an interval of 5 min of resting between measurements, from the right arm, using a mercury sphygmomanometer by auscultatory methods. During the 30 min. preceding the measurements, the subjects were asked to refrain from smoking or drinking caffeinated beverages.

**Laboratory Investigations:**

All subjects were asked to abstain from food intake for at least 12 hours. Blood samples (10 ml, in two aliquots - one aliquot in EDTA and another without anti-coagulant for each participant) - were collected by venipuncture for the analysis of serum lipids [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL)] by standard clinical biochemistry laboratory assays and for glycemia by the hexokinase method with a Dade Behring reagent on a Dimension (Dade Behring) instrument. Serum level of adiponectin by a commercial ELISA (human adiponectin ELISA kit, B-Bridge International Inc.) was also estimated according to the manufacture's instruction.

**Diagnosis of the metabolic syndrome:**

The International Diabetes Federation (IDF) guidelines were used for the diagnosis of the metabolic syndrome, i.e., a central obesity, defined as waist circumference equal to or more than 94 cm and 80 cm (IDF cutoff level recommendations for Middle-Eastern men and women respectively) plus two or more of the following four factors: *1*) raised concentration of triglycerides: ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality; *2*) reduced concentration of HDL cholesterol: <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women or specific treatment for this lipid abnormality; *3*) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; and *4*) raised fasting plasma glucose concentration ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes (Alberti et al., 2005).

**Statistical analysis**

All data were analyzed using the Statistical Program for Social Sciences 11.0.1 software (SPSS for Windows, 2001).

## Results

The patients group consisted of 31 men and 19 women, with a mean (± SD) age of 37.0 (±13.571) years. Table (1) compares between the demographic characteristics of patients and controls. The patients group was divided into 26 patients (17 men) with an early illness and 24 patients (14 men) with a chronic illness. The clinical characteristics of early illness and chronic illness groups of patients are given in table (2) which demonstrates that the two groups were not significantly different in their PANSS scores nor in their usage of antipsychotics. Almost all patients (48 patients; 96%) were receiving antipsychotic polytherapy, with 15 patients on typical antipsychotics alone, 19 patients on atypical antipsychotics alone and 14 patients on both typical and atypical (mixed) antipsychotics. Only one patient was on olanzapine alone and another patient was on risperidone alone. Table (3) shows no significant differences between the early illness and chronic illness groups as regard the prevalence of the metabolic syndrome or its parameters. None of the 19 patients (12 males; 7 females) and the five controls (3 males; 2 females) who met the criteria of the metabolic syndrome was previously diagnosed or treated for this condition or for any of its components. Patients, in comparison to controls, showed significantly increased values of all the parameters of the metabolic syndrome (table 4). These differences were observed whether patients were in the early illness group, or in the chronic illness group. Thus, the number of patients with metabolic syndrome, in the former group (N= 8), and in the latter group (N= 11), were significantly higher than that of the controls ($\chi^2$ =14.809; df= 1; $p$ =0.000 and, $\chi^2$ =28.716; df= 1; $p$ =0.000, respectively). In contrast, however, schizophrenic patients had significantly lower adiponectin level than controls (22.6 ± 8.459 vs. 30.1 ± 6.829 ng/ml; t= 5.853; df= 148; $p$=0.000). Women tended to have a higher serum adiponectin level than men. This difference reached a statistically significant level in the chronic illness group (table 5). Comparison between serum adiponectin levels, by metabolic syndrome (table 6), showed that those who got the syndrome, whether they were schizophrenic patients or controls, had significantly lower levels than those without the syndrome. In a correlation analysis, serum adiponectin level in the patients group was negatively associated with all the parameters of the metabolic syndrome except the HDL level with which it was positively associated (table 7). In the control group, however, there were no such significant correlations.

Patients, classified by the type of antipsychotic medications they were on, did not significantly differ in demographic or clinical characteristics, and as shown in table (8) they did not also differ in their serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters.

**Table (1)** Demographic characteristics of patients and controls

| Characteristic | Patients (N= 50) | Controls (N= 100) | Analysis |
|---|---|---|---|
| Gender: Male: N (%) | 31 (62.0) | 62 (62.0) | $\chi^2 = 0.000$; df= 1; $p = 1.00$ |
| Age (years): | | | |
| Mean (± SD) | 31.6 (10.940) | 31.8 (10.808) | t= 0.112; df= 148; $p$ =0.473 |
| Education (years): | | | |
| Mean (± SD) | 11.3 (2.809) | 11.9 (2.210) | t= 1.477; df= 148; $p$ =0.142 |
| Employment: | | | |
| Employed: N (%) | 14 (28) | 39 (39) | $\chi^2$ =1.755; df= 1; $p$ =0.184 |
| Marrital satus: | | | |
| Married: N (%) | 17 (34) | 45 (45) | $\chi^2$ =1.663; df= 1; $p$ =0.197 |

**Table (2)** Clinical characteristics of patients

| | Early illness group (N= 26) | Chronic illness group (N= 24) | Analysis |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Age, years: Mean | 23.4 | 40.5 | t= 8.915; |
| (± SD) | (2.872) | (9.330) | df= 48; $p$ =0.000 |
| Duration of illness, | | | |
| months: Mean | 14.7 | 189.2 | t= 12.488; |
| (± SD) | (10.288) | (70.505) | df= 48; $p$ =0.000 |
| Age at illness onset, | | | |
| years: Mean | 20.2 | 22.0 | t= 1.606; |
| (± SD) | (2.344) | (5.188) | df= 48; $p$ =0.115 |
| PANSS score | | | |
| Total: Mean | 78.5 | 84.0 | t= 1.491; |
| (± SD) | (13.984) | (11.885) | df= 48; $p$ =0.142 |
| Positive: Mean | 18.6 | 19.1 | t=0.433; |
| (± SD) | (2.246) | (2.112) | df= 48; $p$ =0.667 |
| Negative: Mean | 18.3 | 19.5 | t=1.557; |
| (± SD) | (2.513) | (2.536) | df= 48; $p$ =0.126 |
| Antipsychotics | | | |
| Typical: N | 10 | 5 | |
| Atypical: N | 8 | 13 | $\chi^2$ =3.068; |
| Mixed: N | 8 | 6 | df= 2; $p$ =0.216 |

**Table (3)** Prevalence of metabolic syndrome and its parameters in patients

| Parameters | Early illness group | | Chronic illness group | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | |
| | 26 | (100) | 24 | (100) | Analysis |
| Waist (M ≥ 94, F ≥ 80) | 15 | (57.7) | 17 | (70.8) | $\chi^2$ =0.935; df= 1; $p$ =0.333 |
| BP (≥ 130/85) | 11 | (42.3) | 12 | (50.0) | $\chi^2$ =0.297; df= 1; $p$ =0.586 |
| Glucose (≥ 100 mg/dl) | 13 | (50.0) | 11 | (45.8) | $\chi^2$ =0.087; df= 1; $p$ =0.768 |
| TG (≥ 150 mg/dl) | 10 | (38.5) | 10 | (41.7) | $\chi^2$ =0.053; df= 1; $p$ =0.817 |
| HDL (M<40 mg/dl, F<50 mg/dl) | 11 | (42.3) | 13 | (54.2) | $\chi^2$ =0.703; df= 1; $p$ =0.402 |
| Metabolic syndrome | 8 | (30.8) | 11 | (45.8) | $\chi^2$ =1.202; df= 1; $p$ =0.273 |

**Table (4)** Prevalence of metabolic syndrome and its parameters in patients compared with controls

| Parameters | Patients | | Controls | | Analysis |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | |
| | 50 | (100) | 100 | (100) | |
| Waist (M ≥ 94, F ≥ 80) | 32 | (64) | 46 | (46) | $\chi^2$ =4.327; df= 1; $p$ =0.038 |
| BP (≥ 130/85) | 23 | (46) | 18 | (18) | $\chi^2$ =13.157; df= 1; $p$ =0.000 |
| Glucose (≥ 100 mg/dl) | 24 | (48) | 7 | (7) | $\chi^2$ =34.176; df= 1; $p$ =0.000 |
| TG (≥ 150 mg/dl) | 20 | (40) | 11 | (11) | $\chi^2$ =17.098; df= 1; $p$ =0.000 |
| HDL (M<40 mg/dl, F<50 mg/dl) | 24 | (48) | 9 | (9) | $\chi^2$ =29.545; df= 1; $p$ =0.000 |
| Metabolic syndrome | 19 | (28) | 5 | (5) | $\chi^2$ =27.009; df= 1; $p$ =0.000 |

**Table (5)** Serum adiponectin levels (ng/mL) in patients and controls, by sex

| | N | Mean | (± SD) | Analysis |
|---|---|---|---|---|
| Patients: | 50 | 22.6 | (8.459) | |
| Male | 31 | 20.8 | (7.679) | |
| Female | 19 | 25.4 | (9.088) | t= 1.923; df= 48; *p* =0.060 |
| Early illness group | 26 | 22.8 | (8.266) | |
| Male | 17 | 23.2 | (8.095) | |
| Female | 9 | 24.0 | (7.616) | t= 0.252; df= 24; *p* = 0.803 |
| Chronic illness group | 24 | 22.5 | (9.422) | |
| Male | 14 | 17.9 | (6.257) | |
| Female | 10 | 26.7 | (10.478) | t= 2.568; df= 22; *p* =0.018 |
| Controls | 100 | 30.1 | (6.829) | |
| Male | 62 | 29.8 | (6.185) | |
| Female | 38 | 30.2 | (7.487) | t= 0.320; df= 98; *p* = 0.750 |

Table (6) Mean (± SD) of serum adiponectin level (ng/mL) in patients and controls, by metabolic syndrome

| | | Metabolic Syndrome | | |
|---|---|---|---|---|
| | | Present | Not present | Analysis |
| Patients: | N | 19 | 31 | |
| | Mean | 14.7 | 27.4 | |
| | (± SD) | (±2.130) | (±7.186) | t= 7.430; df= 48; *p* = 0.000 |
| Controls: | N | 5 | 95 | |
| | Mean | 23.8 | 30.4 | |
| | (± SD) | (±10.733) | (±6.481) | t= 2.144; df= 98; *p* = 0.034 |
| Total: | N | 24 | 126 | |

| | | | |
|---|---|---|---|
| Mean (± SD) | 16.6 (±6.142) | 29.7 (±6.761) | t= 8.770; df= 148; $p$ = 0.000 |

Table (7) Pearson's correlation coefficients between adiponectin and the parameters of the metabolic syndrome

| Criteria | Adiponectin | | | |
|---|---|---|---|---|
| | Patients | | Controls | |
| | r | ($p$) | r | ($p$) |
| Waist | -0.295 | (0.038) | -0.174 | (0.084) |
| BP (systolic) | -0.282 | (0.047) | -0.085 | (0.400) |
| BP (diastolic) | -0.280 | (0.049) | -0.012 | (0.903) |
| Glucose | -0.388 | (0.005) | -0.073 | (0.471) |
| HDL | 0.448 | (0.001) | 0.010 | (0.925) |
| TG | -0.295 | (0.038) | -0.127 | (0.209) |

Table (8) Adiponectin and parameters of the metabolic syndrome in the patients group, by antipsychotic treatment

| | Antipsychotic Treatment | | | |
|---|---|---|---|---|
| | Typical (N= 15 ) | Atypical (N= 21) | Mixed (N= 14) | |
| | Mean (± SD) | Mean (± SD) | Mean (± SD) | ANOVA |
| Adiponectin | 24.5 (8.895) | 19.6 (8.035) | 23.4 (8.897) | F= 1.245 $p$= 0.297 |
| Waist | 99.9 (13.191) | 109.2 (17.147) | 105.9 (18.821) | F= 1.245 $p$= 0.297 |
| BP (systolic) | 133.7 (19.682) | 136.8 (19.376) | 136.0 (19.914) | F= 0.100 $p$= 0.905 |
| BP (diastolic) | 87.3 (12.228) | 89.3 (11.542) | 88.2 (10.116) | F= 0.131 |

| | | | |
|---|---|---|---|
| | | | $p$= 0.877 |
| Glucose | 97.9 (24.828) | 111.7 (26.163) | 105.7 (31.796) | F= 1.149 |
| | | | $p$= 0.326 |
| HDL | 47.4 (11.219) | 42.8 (15.562) | 44.4 (14.515) | F= 0.533 |
| | | | $p$= 0.590 |
| TG | 131.1 (56.914) | 144.0 (36.797) | 138.2 (45.656) | F= 0.342 |
| | | | $p$= 0.712 |

**Discussion**

To our knowledge, this is the first study from Egypt to show a high prevalence of the metabolic syndrome and its components among patients diagnosed with schizophrenia compared to normal subjects. In this study, 28% of the patients with schizophrenia fulfilled the IDF criteria for the diagnosis of metabolic syndrome, as opposed to only 3% of the matched apparently healthy comparison subjects ($p$= 0.000). Despite methodological differences, our findings are generally in line with those from other countries. Thus, in USA, for example, using baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, according to National Cholesterol Education Program (NCEP) criteria, metabolic syndrome was found to be highly prevalent (40.9%) in schizophrenia patients (McEvoy et al., 2005), and in another American study, the prevalence of the metabolic syndrome was as high as 51.2% among veterans with schizophrenia (Meyer et al., 2006). In Cuba, using the NCEP criteria, the prevalence of the metabolic syndrome was even higher (63%) in all patients with schizophrenia (41% in non-Hispanic patients and 74% in Hispanic patients) (Kato et al., 2004). In Northern Sweden, the prevalence of the metabolic syndrome among a cohort of patients with schizophrenia, according to the NCEP criteria, was 34.6% (Hagg et al., 2006). In Finland, also using the NCEP criteria, in a population-based birth cohort, 19% of the schizophrenic patients were found to have a metabolic syndrome, a 4-fold greater risk than the general population (Saari et al., 2005). Our figures, though lower than some of those found in the American and European studies, should still be considered as seriously high. Our concern is also because of the observation that there was a complete failure to detect, and hence to adequately treat, the metabolic syndrome or its components before admission to the study. Our observation, however, is in line with those of other investigators, e.g., Bo et al. (2007) who reported that more than 97% of unknown metabolic syndrome cases in their series would be identified among apparently healthy individuals when overweight/obese, and normal-BMI subjects with low physical activity were screened. Abdul-Ghani et al. (2005) found that approximately 70% of the overweight Arab population in Israel has either undiagnosed metabolic syndrome or abnormal glucose metabolism. Athyros et al. (2005) suggest that metabolic syndrome is not recognised among the general

population (in Greece), and therefore, treatment and control of the syndrome and its component conditions are extremely low. Studies from various countries (e.g., Csaszar et al., 2006; Gupta et al., 2004; Tanchoco et al., 2003), including Arab countries (e.g., Al-Lawati et al., 2003; Bouguerra et al., 2006;), underscore the need for a more thorough screening in high-risk populations (Straker et al., 2005). Clearly, schizophrenic patients treated with antipsychotics ought to be considered at high risk of developing metabolic syndrome (Correll et al., 2007; Newcomer, 2004), as is confirmed by the current data. Concern about these metabolic abnormalities in schizophrenic patients is not only because of their direct, somatic effects on morbidity and mortality, but also because of their suspected association with lower adherence to medication (Weiden et al., 2004) which is equally problematic for both antipsychotic and nonpsychiatric medications (Dolder et al., 2003).

The reasons why individuals with schizophrenia are more prone to developing diabetes and metabolic syndrome than the general population remain controversial (Holt et al., 2005), but likely to be multifactorial (Fowler et al., 2005; Kahl, 2005). In the current study, the higher prevalence of metabolic syndrome and its components in patients, as compared to control subjects, was already present in the early illness group (age range: 18- 30 years), indicating a greater vulnerability to develop metabolic syndrome in patients with schizophrenia. The maintenance of having such high prevalence in the chronic illness group (age range: 31- 60 years), as compared to control subjects, suggests a long-term direct impact of the schizophrenic illness and/or negative metabolic side-effects of prolonged antipsychotic medication. This suggestion is in line with other studies (e.g., De Hert et al., 2006; Vivian, 2006). Many reports claim that second-generation antipsychotics can increase the risk of metabolic abnormalities in patients with schizophrenia (Newcomer and Haupt, 2006; Reist et al., 2007; Tarricone et al., 2006). While some researchers regarded that the situation is far from clear as regard the potential risk associated with different antipsychotic drugs (Rouillon and Sorbara, 2005), others maintained that there are obvious differential effects of second-generation antipsychotics on metabolic parameters (Haupt, 2006; Henderson et al., 2005; Lamberti et al., 2006). According to a recent US consensus statement (American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity, 2004), the second-generation antipsychotics vary in their propensity to cause obesity, hyperglycaemia and hyperlipidaemia, with clozapine and olanzapine showing the greatest effects, risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having lower effects. On the other hand, European (Expert group 'Schizophrenia and Diabetes 2003', 2004) and Australian (Lambert et al., 2004) consensus statements did not recognize any difference among the second-generation antipsychotics as to their propensity to cause metabolic side effects. Moreover, the American consensus statement itself acknowledges the caveat that aripiprazole and ziprasidone have fewer long-term data due to the limited amount of time they have been on the market (American Diabetes Association; American Psychiatric Association; American Association of Clinical

Endocrinologists; North American Association for the Study of Obesity, 2004). In contrast to these and other reports (e.g., Mackin et al., 2005; Wu et al., 2006) which associate metabolic syndrome more strongly with prescription of atypical antipsychotics than with prescription of typical neuroleptics, our data failed to differentiate between the typical and atypical treated groups in terms of prevalence of metabolic syndrome or its parameters. Our findings, however, may get some support from the study by Guha et al. (2005) which compared the prevalence of hyperglycaemia in Indian schizophrenic patients taking olanzapine with those taking typical antipsychotics (either haloperidol or trifluoperazine) but found no significant difference. Another study in support of our findings, reported no differential diabetogenic effect of antipsychotic treatment, irrespective of its type (typical or atypical) in a sample of European schizophrenics who were mostly on monotherapy (Cohen et al., $2006_b$). However, studies comparing patients receiving antipsychotic monotherapy, with patients on antipsychotic polytherapy, showed that the latter group had higher rates of metabolic syndrome and lipid markers of insulin (Correll et al., 2007). In the current study, comparison between the effects of antipsychotic monotherapy and polytherapy was not possible since almost all patients (96%) were on polytherapy.

Although insulin resistance is thought to be central abnormality in the pathogenesis of metabolic syndrome (Bigazzi and Bianchi, 2007; Teede et al., 2006), insulin resistance is elusive, perhaps more easily identified than measurable (Samaras et al., 2006). The WHO classification of the metabolic syndrome includes insulin resistance, but only when measured by hyperinsulinaemic euglycaemic clamp with comparison to normative background population ranges. The clamp requires bilateral cannulation, arterialisation of blood flow to the vein, 2 hours of measures, and experience. Obtaining normative sex- and ethnic-specific population data for comparison is another difficulty. Other techniques such as the frequently sampled intravenous glucose tolerance test (Pacini et al., 1986), and the insulin suppression test (Harano et al., 1977; Shen et al., 1970) are similarly complicated and cumbersome. Simpler alternative estimates have evolved, of which the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985) has been the most widely used, but neither it nor any of the others has become the standard for diagnosing insulin resistance (Stern et al., 2005). In the present study, the metabolic syndrome was diagnosed according to the International Diabetes Federation (IDF) criteria which do not include an assessment of insulin resistance. This omission by the IDF was not surprising because specific measurements of insulin resistance are not clinically practical (Samaras et al., 2006). We did not assess the insulin resistance in this study, but we were interested in the major adipokine secreted by fat cells, the adiponectin, irrespective of its 'complex relationship with insulin resistance' (Abbasi et al., 2004; Spranger et al., 2004). Thus, we examined the association of serum adiponectin with the parameters of the metabolic syndrome in the schizophrenic patients. Our data clearly showed that that those with the metabolic syndrome, had significantly lower levels of serum adiponectin than those without it. The difference noted between schizophrenic patients and controls could be explained by the much higher prevalence of the

metabolic syndrome among these patients. Our observation that women, especially in the chronic illness group, tended to have a higher serum adiponectin level than men is supported by some studies (Arita et al., 1999; Philip et al., 2003) but not by all other studies (Ryan et al., 2003; Weyer et al., 2001). However, our observation can be explained by the fact that women tend to have less visceral fat tissue than subcutaneous fat (Wajchenberg, 2000). Recent evidence showed that serum adiponectin levels are determined predominantly by visceral and not by subcutaneous fat (Kwon et al., 2005; Steffes et al., 2006).

Many studies have shown that there may be an adiposity-hypothalamus axis designed to maintain and regulate energy balance in humans. Adiponectin is one of the important peptides associated along with this axis (Leibowitz and Wortley, 2004; Meier and Gressner, 2004; Trayhurn, 2005). Dysregulation of this axis may contribute to obesity and the development of hyperinsulinemia, which is associated with insulin resistance and diabetes (Stefan et al., 2002; Weyer et al., 2001). Development of a method for convenient prediction of metabolic syndrome in daily clinical practice presents a major challenge. From this study, we found that serum adiponectin levels were inversely associated with metabolic risk profiles in Egyptian patients with schizophrenia. This is in line with the mounting body of evidence in other populations to suggest that adiponectin is an insulin-sensitizing hormone and that the plasma level of this hormone is a predictor of the subsequent development of type 2 diabetes and metabolic syndrome (Gilardini et al., 2006; Krakoff et al., 2003).

The alterations in serum adiponectin concentration in schizophrenic patients during treatment with olanzapine or risperidone have been reported (Togo et al., 2004). However, we did not find significant differences in the serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters between patients receiving typical, atypical or mixed antipsychotics.

In addition to the lack of an assessment of insulin resistance, certain shortcomings of our study should be mentioned. The results of our study need to be interpreted within the limitations of its cross-sectional design, moderate sample size and lack of power to examine individual antipsychotic combinations. All patients were already under treatment before inclusion into the study, and thus, we could not have a drug naïve group for comparison. In a recent preliminary study, however, Cohn et al. (2006) reported insulin resistance and susceptibility to type 2 diabetes in patients with schizophrenia who are free of antipsychotic drugs. Despite these limitations, our results should encourage clinicians who treat patients with schizophrenia to monitor for the parameters that define the metabolic syndrome as part of the ongoing management of patients treated with antipsychotics. In line with the mounting body of evidence in other populations, this study indicates that measurement of serum adiponectin level by ELISA technique may be a useful biomarker for the metabolic syndrome in schizophrenic patients.

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## متلازمة الأيض و مستوى المصل للأديبونيكتين في مرضى الفصام المصريّين

**الخلفية:** متلازمة الأيض عامل مخاطرة هام في معدّلات الإصابة و الوفيات بأمراض القلب و الأوعية الدموية في المرضى الفصاميين. بيد أن معدلات انتشارها في مصر بين هذه المرضى غير مؤكدة. كذلك فإن المعرفة قليلة عن العلاقة بين متلازمة الأيض و مستوى المصل لمادة مثل الأديبونيكتين لدى مرضى الفصام المصريين، بينما تجذب الآن فائدة الأديبونيكتين في التنبؤ بمقاومة الأنسولين ومتلازمة الأيض لدى المجتمعات الأخرى انتباها كبيرا.

**الأغراض:** تقييم معدلات انتشار متلازمة الأيض و مستوى المصل للأديبونيكتين لدى عيّنة من مرضى العيادة الخارجية المصريين المصابين بالفصام مختبرين فرضين (أ ) أن انتشار متلازمة الأيض أعلى بين المرضى الفصاميين بالمقارنة بمجموعة طبيعية من الأشخاص، و ( ب) أن علاقة مستوى الأديبونيكتين بالمصل مع العوامل المحددة لمتلازمة الأيض علاقة عكسيّة لدى هؤلاء المرضى.

**الطرق:** صنّف خمسين مريضا فصاميا متتاليا بالعيادة الخارجية إلي مجموعتي المرضى المبكّر (٢٦مريضا ) و المرض المزمن (٢٤ مريضا ) ، و قورنوا بمجموعة ضابطة من مائة شخص سليم ظاهريا، وذلك باستخدام معايير الاتحاد الدولي لمرض السكر ومستويات الأديبونيكتين بالمصل.

**النتائج:** حقق ٢٤٪ من المرضى ( ٥ ) في مقابل خمسة من المجموعة الضابطة ( ٥ ) معايير متلازمة الأيض. لكن الاختلاف في معدلات انتشار هذه المتلازمة و معاييرها بين مجموعتي المرضى (المبكّر و المزمن) لم يكن ذات مغزى. كما لوحظ أن أحدا من هؤلاء المرضى أو من المجموعة الضابطة قد سبق وشُخّص أو عُولج من هذه المتلازمة أو من أيّ من عناصرها. وكان مستوى الأديبونيكتين بالمصل في مجموعة المرضى مرتبطا ارتباطا سلبيا بكلّ معايير متلازمة الأيض باستثناء مستوى البروتين الدهني عالي الكثافة إذ كان ارتباطه موجبا. أما في المجموعة الضابطة فلم تبرز هذه الإرتباطات مستويات ذات مغزى. كذلك لم يختلف المرضى، بتصنيفهم وفقا لنوع العلاج بمضادات الذهان، من حيث مستوى الأديبونيكتين بالمصل، أو معدلات انتشار متلازمة الأيض أو عناصرها.

**الاستنتاجات:** تنتشر متلازمة الأيض بدرجة كبيرة بين مرضى الفصام المصريين الذين يتلقون علاجهم. من ثمّ، يجب أن يكون تقييم و متابعة عوامل المخاطر المرتبطة بمتلازمة الأيض جزء من العمل الإكلينيكي مع هؤلاء المرضى. وقد جاءت هذه الدراسة متمشية مع الدليل المتزايد في المجتمعات الأخرى ولتبيّن أن قياس مستوى الأديبونيكتين بالمصل بطريقة "إليسا" قد يكون مؤشرا حيويا مفيدا لمتلازمة الأيض في مرضى الفصام.