Metabolic syndrome and type 2 diabetes in chronic institutionalized patients with schizophrenia

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Introduction

Schizophrenia is a life-threatening illness with a mortality rate that is twice as high as that of the general population. Over 60% of deaths in schizophrenic patients are due to natural causes such as cardiovascular illness. Patients with schizophrenia and schizoaffective or bipolar disorder may have a predisposition to metabolic syndrome that is exacerbated by a sedentary life, poor dietary habits, possible limited access to care, and antipsychotic drug-induced adverse effects. It has been found that the prevalence rate of metabolic syndrome among schizophrenic patients ranges from 32 to 51%, with a two- to three-fold higher mortality rate due to heart attack compared with those without metabolic syndrome.

Aim and objectives

The current study aimed at detecting the prevalence and patterns of metabolic syndrome in chronic institutionalized patients with schizophrenia, comparing patients with metabolic syndrome - defined by different criteria- and lastly trying to find the predictor factors for metabolic syndrome and for diabetes mellitus.

Methods

Ninety-five patients with schizophrenia and schizoaffective disorder were recruited from long-stay hospital wards, were interviewed using structured clinical interview, and were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. They were subjected to a cross-sectional assessment by psychopathological rating scales including positive and negative syndrome scale, mini mental state examination, and clinical global impression – severity index scale and also to anthropometric measurement taking (BMI and waist circumference).
Sociodemographic and clinical characteristics as well as treatment history were collected from data files. Cases were classified into four groups according to the International Diabetes Federation criteria: definite cases with metabolic syndrome (IDF criteria); the high-risk group (lacking one criterion); risky cases with risk for central obesity; and patients with no apparent risk. Data were collected and statistically analyzed.

Results

Twenty-two patients (23.15%) had definite metabolic syndrome according to IDF criteria, 47 patients (49.4%) had high risk, 17 patients (17.8%) had risk factors of metabolic syndrome, and only nine cases (9.4%) had no apparent risk for metabolic syndrome. Sociodemographic and clinical characteristics and psychopathological rating scores were not predictors for metabolic syndrome, nor for diabetes mellitus. BMI and waist circumference had the highest sensitivity, predictive value, and diagnostic accuracy for metabolic syndrome compared with the presence of diabetes, hypertension, or dyslipidemia. Diabetes mellitus occurred earlier and was of longer duration compared with other metabolic disturbances.

Conclusion

(1) The high risk of MS among patients with chronic schizophrenia mandates careful monitoring and elimination of risk factors.
(2) BMI and WC as well as blood sugar and lipid profile are considered simple measures for detecting risk factors.
(3) Attempts towards toward eliminating risk factors such as poor lifestyle, obesity, and metabolic disturbances is vital for long stay hospitalised patients.

Keywords:
cardiovascular disease, diabetes mellitus, metabolic syndrome, schizophrenia

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Introduction

The metabolic syndrome (MS) encompasses a cluster of metabolic risk factors associated with increased risk for type 2 diabetes mellitus and cardiovascular diseases (Black and Fisher, 1992; Sattar *et al*., 2003). It has been defined as the presence of three of five quantitatively defined markers: abdominal obesity, high triglyceride levels, low level of HDL cholesterol, high blood pressure, and elevated fasting glucose levels (Adult Treatment Panel III, 2001).

The prevalence of MS has varied from 10 to 22% (Ford *et al*., 2002). Vanhala *et al.* (1997) reported that the prevalence of MS was 8% in women and 17% in men. It is estimated that around a quarter of the world's adult population suffer from this syndrome (Dunstan *et al*., 2002) and they are twice as likely to die from it and three times as likely to have a heart attack (Isomaa *et al*., 2001). In addition, patients suffering from this syndrome have a five-fold higher risk of developing type 2 diabetes (Stern *et al*., 2004). The clustering of cardiovascular disease (CVD) risk factors that typify the MS is now considered to be the driving force behind the CVD epidemic.

Schizophrenia has a mortality rate that is twice as high as that of the general population (Brown, 1997). It was found that life expectancy among schizophrenic patients is 20% shorter than that of the general population (Newman and Bland, 1991) and those who are in their 40s have a life expectancy that is 6–7 years lower than that of the general population (Hannerz *et al*., 2001). Over 60% of the deaths in schizophrenic patients are due to natural causes such as cardiovascular illness (Brown *et al*., 2000).

Prevalence of type 2 diabetes varied between 6 and 21%, being two- to three-fold higher among patients with schizophrenia than in the general population (American Diabetic Association, 2004; Cohen *et al*., 2006).

Impaired fasting glucose tolerance was found in first-episode drug-naive patients with schizophrenia, suggesting that defective regulation of glucose may be partially associated with the disease process (Ryan *et al*., 2003). Many factors may contribute to increased risk for MS, diabetes mellitus, and CVD in this population – for example, their eating behaviors, exercise habits, lifestyle, history of glucose dysregulation, pre-existing hypertension, and drug use (Brown *et al*., 1999; Kane *et al*., 2004).

Antipsychotics are an important component in the medical management of many psychotic conditions. With the introduction of second-generation antipsychotics in the last decade the use of these medications has soared. Although they have many benefits compared with their early counterparts, their use has been associated with reports of marked weight gain, diabetes, and an atherogenic lipid profile; however, the relative contribution of second-generation antipsychotics to MS in patients with schizophrenia is unclear (Henderson, 2002).

The current study aimed at detecting the prevalence and patterns of metabolic syndrome in chronic institutionalized patients with schizophrenia, comparing patients with metabolic syndrome - defined by different criteria- and lastly trying to find the predictor factors for metabolic syndrome and for diabetes mellitus.

Methods

The study was conducted during the first 6 months of 2010 at the Psychological Medicine Hospital, Kuwait. This is the only psychiatric hospital in the State of Kuwait. It has five general units, in addition to one rehabilitation, one forensic, one geriatric, casualty, and child psychiatry unit, and an addiction center.

There are six long-stay hospital wards (five wards for male and one ward for female patients) with a total capacity of 132 beds.

Approval by the local hospital ethical committee was a prerequisite.

Sampling and participants

All patients in the long-stay hospital wards, with at least 6 months of hospital stay at their last admission, were screened.

Inclusion criteria: Patients suffering from schizophrenia or schizoaffective disorder, of both sexes, who were over 18 years of age and who had provided an informed consent, either by themselves or through a relative, were eligible for being inclusion in the study.

Exclusion criteria: patients with mental subnormality, organic brain syndrome, patients receiving diabetogenic drugs such as corticosteroids, and those with long periods of absence from the hospital (> 3 months) during the last year were excluded.

A total number of 126 patients were examined; 31 patients were excluded (23 had mental retardation, two women suffered from psychosis due to epilepsy, one had bipolar disorder, one woman had mixed personality disorder, two men were absent from the hospital for more than 3 consecutive months, and two men refused to give consent). The resultant 95 patients had been institutionalized for a considerable period of time under the same living conditions and lifestyle, including balanced diets, restricted smoking, and sport activity.

Procedure

The design of the current study consisted of two parts: first, all files of the selected cases were retrospectively reviewed and data pertaining to their sociodemographics, clinical examination, treatment history, mental state with review of their medications, medical history, current investigations, and a cross-sectional study in which patients had to be interviewed using a structured clinical interview in order to be diagnosed according to the *Diagnostic and Statistical Manual of Mental illness 4th ed*. were collected. All recruited patients had to have measurements taken of their vital signs, BMI, and waist circumference (WC). They were then subjected to the following psychometric assessments: positive and negative syndrome scale (PANSS; Kay *et al*., 1986), mini mental state examination

(MMSE; Folstein *et al.*, 1975), and clinical global impression – severity index scale (CGIS; Guy and Bonato, 1970).

Defining metabolic syndrome

There are different criteria for defining MS such as those stated in the International Diabetes Federation IDF (2006), the WHO 1999, the American Medical Association (2001), and the updated NCEP (2001).

As there is lack of epidemiological data for defining central obesity with specific cutoff points for eastern Mediterranean and Middle East (Arab) and Gulf populations, modified criteria for definitions of MS were used by the researchers, dividing patients into four groups according to their pragmatic BMI and WC cutoff points.

Patients with definite metabolic syndrome

Patients were diagnosed with MS if their central obesity was indicated by WC greater than or equal to 102 cm (40 inches) in the case of men or greater than or equal to 88 cm (35 inches) in the case of women and/or BMI was greater than or equal to 30; and when they fulfilled two of the following four conditions: blood sugar level greater than or equal to 5.6 mmol/l, blood pressure level greater than or equal to 130/85, elevated triglyceride levels greater than or equal to 1.7 mmol/l, reduced HDL levels of less than 1.03 mmol/l for men and less than 1.29 mmol/l for women, or if they were under treatment for any of the above-mentioned conditions (IDF criteria).

Patients with high-risk metabolic syndrome

Patients were diagnosed with high-risk MS when their WC and/or BMI cutoff points were as mentioned before and they fulfilled only one criterion from those of blood sugar, blood pressure, or lipid disturbances or being on treatment for it.

Patients at risk for metabolic syndrome

Patients were diagnosed as being at risk for MS when their WC cutoff points were greater than the range of 94–101.9 for men or greater than the range of 84–87.9 for female patients and/or their BMI was between 25 and 29.9 with or without disturbances in blood sugar, blood pressure, or lipid profile.

Patients with a normal metabolic state

Patients with a WC of less than 94 cm for men or less than 84 cm for women, BMI less than 25, and with no disturbances in blood pressure, blood sugar level, or lipid profile, nor undergoing treatment for the same, were reported as having a normal metabolic state.

Statistical analysis

Data were collected and coded. They were then entered into an IBM compatible computer, using SPSS version 17 (IBM; Illinois, Chicago, USA). The entered data were checked for accuracy and normality using the Kolmogorov–Smirnov test. Qualitative variables were expressed as number and percentage and quantitative variables as mean ($\bar{x}$) and SD. The arithmetic mean ($\bar{x}$) was used as a measure of central tendency and SD as a measure of dispersion.

The following statistical tests were used:

The independent sample *t*-test was used as a parametric test of significance for comparison between two sample means after conducting Levene's test for determining equality of variances.

The χ^2 test (or the likelihood ratio) was used as a nonparametric test of significance for comparison between the distribution of two qualitative variables.

Fisher's exact test, which yields a *P* value directly, was used as a nonparametric test of significance for comparison between the distributions of two qualitative variables whenever the χ^2 test was not appropriate.

A paired sample *t*-test was used as a parametric test of significance for comparison between the before and after values of quantitative variables.

The one-way analysis of variance (*F*-test) was used as a parametric test of significance for comparison between more than two sample means using either Scheffe's or Tauhane's post-hoc tests for homogeneity testing.

The Pearson correlation coefficient (*r*) was used as a parametric measure of the mutual relationship between two normally distributed quantitative variables.

Validating parameters – sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA) – were calculated for the individual criteria of MS in patients with chronic schizophrenia:

sensitivity = the ability of the test to detect those with the condition;
specificity = the ability of the test to exclude those without the condition;
PPV = the ability of the test to detect those with the condition among those positively screened;
NPV = the ability of the test to exclude those without the condition among those negatively screened;
DA = the percentage of total agreement of both methods with respect to true positives and true negatives.

Multivariable logistic regression analysis for prediction of MS and diabetes mellitus.

A 5% level was chosen as the level of significance in all statistical significance tests.

Results

Comparison between patients with metabolic syndrome defined by different criteria and those with a normal metabolic profile

On applying the IDF criteria on the 95 patients included in the study, 22 patients (23.15%) were found to have definite MS, 47 (49.4%) were identified as high-risk

Table 1 Sociodemographics of patients with different criteria defining metabolic syndrome and patients with a normal metabolic profile

		Metabolic syndrome				
	Normal metabolic profile ($n=9$)	Risky ($n=17$)	High risky ($n=47$)	Definite ($n=22$)	Total ($n=95$)	Person $\chi^2(3)$ LLR $\chi^2(3)$
Sex						
Female	0	0	11	4	15	
Male	9	17	36	18	80	0.01*
Marital status						
Single	9	11	36	12	68	
Married	0	2	3	7	12	
Divorced	0	3	7	3	13	0.07
Widow	0	1	1	0	2	
Job						
Jobless	7	12	36	14	69	
Professional	0	0	1	0	1	0.78
Retired	2	5	10	8	25	
Education						
Illiterate	3	5	9	5	22	
Low grade	5	9	27	12	53	
High grade	1	3	9	4	17	0.97
University	0	0	2	1	3	
Socioeconomic status						
Very low	1	4	14	7	26	
Low standard	8	10	31	11	60	0.30
Moderate	0	3	2	3	8	
Highly moderate	0	0	0	1	1	

LLR, likelihood ratio.
*Significant if $P<0.05$.

cases, 17 (17.8%) were identified as risky patients, and only nine patients (9.4%) were identified as having a normal metabolic profile. Definite and high-risk cases for MS were significantly more among men and found only in exclusive cases among women ($P=0.01$). No other significant difference was observed between the studied groups with respect to their sociodemographic status (Table 1).

Definite cases for MS and high-risk cases were significantly older than those with a normal metabolic profile (51.4 ± 9.8, 51.9 ± 9.3, and 47.9 ± 10.1 years, respectively; $P=0.01$) (Table 2). Moreover, MS was found to be directly correlated with the duration of illness, representing a significant difference between patients with MS and those with a normal metabolic profile ($P=0.04$; Table 2).

Positive symptoms were significantly predominant at the time of onset of schizophrenia, especially in patients with definite MS and/or in patients at high risk compared with other groups ($P=0.05$; Table 3).

As regards the PANSS score, patients with a normal metabolic profile and those who are less prone to MS obtained significantly higher scores on the negative subscale (34.6 ± 9.1 and 33.5 ± 10.5, respectively) compared with patients with definite MS and at high risk ($P=0.007$; Table 2).

No other significant differences were found between patients with MS defined by different criteria and those with a normal metabolic profile as regards CGIS scores ($P=0.42$; Fig. 1), MMSE scores ($P=0.19$; Table 2), or treatment history [type of medication used, either monotherapy or polytherapy ($P=0.62$), conventional antipsychotics or atypical antipsychotics ($P=0.26$)].

Diabetes mellitus and pattern of metabolic disturbances

Among the 95 studied patients, 28 (29.47%) suffered from diabetes, 29 (30.52%) were hypertensive, and 49 (51.57%) had dyslipidemia. The mean duration of diabetes (10.43 ± 7.3 years) was longer than that for hypertension (7.3 ± 5.05 years) or dyslipidemia (4.6 ± 3.4 years).

At onset of medical illness, conventional antipsychotics were used more frequently by patients suffering from diabetes mellitus ($n=16$, 57.14%) or hypertension ($n=18$, 62.07%), whereas atypical antipsychotics were more frequently used by patients who developed dyslipidemia ($n=32$, 56.31%).

Interestingly, the onset of diabetes mellitus, hypertension, and dyslipidemia for most of the cases was during the period of chronic institutionalization, especially at the time of last admission ($n=17$, 60.71%; $n=21$, 72.41%; and $n=40$, 81.63%, respectively). Only one patient with diabetes mellitus and two patients with dyslipidemia were reported before the onset of schizophrenia.

There were no significant differences between diabetic and nondiabetic patients with respect to their sociodemographic features (Table 4), clinical characteristics, MMSE scores (Tables 4–6), CGIS scores (Fig. 2), history of previous use of conventional or atypical antipsychotics ($P=0.38$), or even current treatment type and dose of medications used (Table 7).

As shown in Table 8, most diabetic patients have coincident hypertension ($n=18$, 54.28%; $P=0.000$) or dyslipidemia ($n=22$, 78.57%; $P=0.000$). Moreover, a high percentage of diabetic patients were significantly more obese ($n=20$, 71.42%; $P=0.04$) and had a larger but nonsignificant WC ($n=19$, 67.85%; $P=0.13$).

Table 2 Correlation between patients with metabolic syndrome defined by different criteria and patients with normal metabolic profile according to age, clinical data, and clinical scale scores

		Metabolic syndrome				
	Normal metabolic profile ($n=9$)	Risky ($n=17$)	High risky ($n=47$)	Definite ($n=22$)	Total ($n=95$)	P value
Age (years)	40±10.3	51.9±9.3	47.9±10.1	51.4±9.8	48.9±10.3	0.01*
Age at onset (years)	19±3.9	20.4±4.06	21.2±6.4	22.7±5.4	21.2±5.7	0.34
Duration of illness (years)	19.6±8.3	31.8±9.5	26.5±8.9	28.6±9.5	27.5±9.3	0.04*
Number of relapses	15.8±8.2	20.5±13.1	17.4±12.4	22.6±13.4	19.07±12.5	0.34
Relapse duration (months)	2.6±1.4	3.2±2.4	2.9±1.6	4.7±7.5	3.3±3.9	0.31
Last stay duration (years)	7.9±7.1	10.5±6.9	10.06±6.4	9.5±4.9	9.8±6.2	0.77
Total stay duration (years)	11.0±8.1	17.6±9.6	14.2±6.9	14.8±5.8	14.6±7.4	0.16
MMSE scores	18.8±5.2	16.2±5.5	19.6±7.8	21.0±7.05	19.4±7.1	0.19
PANSS positive subscale score	18.6±7.9	18.6±7.4	17.1±6.9	18.4±6.7	17.8±7.0	0.83
PANSS negative subscale score	34.6±9.1	33.5±10.5	27.9±10.01	23.1±11.4	28.4±10.9	0.007**
BMI	20.7±1.8	26.7±2.03	32.89±6.8	36.9±8.2	31.58±7.8	0.000**
Waist circumference	85.1±4.5	93.50±6.9	103.4±18.2	108.57±26.2	101.1±19.4	0.004**

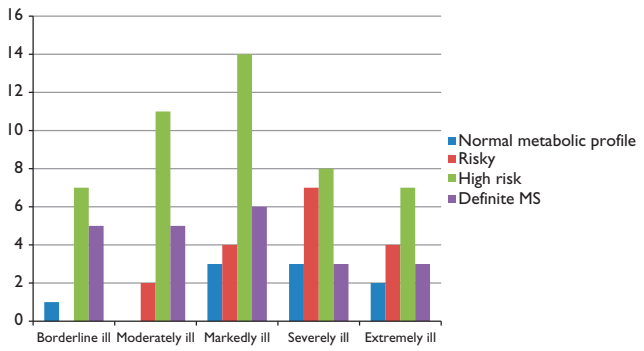
MMSE, mini mental state examination; PANSS, positive and negative syndrome scale.
*Significant if $P<0.05$.
**Highly significant if $P<0.001$

Table 3 Clinical characteristics of patients with metabolic syndrome defined by different criteria and patients with a normal metabolic profile

		Metabolic syndrome				
	Normal metabolic profile	Risky	High	Risky definite	Total ($n=95$)	Person $\chi^2(3)$ LLR $\chi^2(3)$
Symptoms at onset						
Negative	2	0	0	1	3	
Positive	5	14	34	19	72	
Mixed	2	3	13	2	20	0.05*
Total	9	17	47	22	95	
Schizophrenia subtypes						
Residual	1	3	7	3	14	
Undifferentiated	4	9	18	10	41	
Paranoid	2	3	13	4	22	0.92
Disorganized	1	1	7	1	10	
Schizoaffective	1	1	2	4	8	
Family psychiatric history						
Negative	4	9	25	9	47	
Positive	5	8	22	13	48	0.78
Family medical history						
Negative	7	12	33	13	65	
Positive	2	5	14	9	30	0.71

LLR, likelihood ratio.
*Significant if $P<0.05$.

Figure 1



Illness severity among the four studied groups using the clinical global impression severity index (CGIS). Note: the higher the CGIS score, the more severe the illness ($P=0.42$). MS, metabolic syndrome.

The pattern of medical illness (metabolic disturbances)

Figure 3 shows that the median time of onset of diabetes was 20 years after the onset of schizophrenia, but hypertension and dyslipidemia occurred 24 years after the onset of schizophrenia. The mean duration of the schizophrenic course was 27.5 years, and a median duration of 9.8 years of those metabolic disturbances occurred during chronic hospitalization.

Predictive value and diagnostic accuracy for metabolic syndrome criteria

Among all the criteria for MS, BMI (≥25) was the most specific criterion correctly identifying the presence of MS (DA = 78.95). The DA and PPV were higher for MS with BMI of at least 25, followed by male WC or greater than or less than 101 (DA = 73.75). Diabetes mellitus and hypertension were the least reliable criteria for DA or PPV (Table 9).

When each of the following factors, age, sex, socioeconomic standard, family history of diabetes mellitus, hypertension, and dyslipidemia, chronic schizophrenia course, chronic hospitalization, PANSS, MMSE and CGIS scores, were entered in a logistic regression model, none of them were of significant predictive value for the presence of MS or diabetes mellitus (χ^2 model = 21.096, significant $P = 0.02$, $R^2 = 0.318$).

Table 4 Sociodemographics of diabetic (*n* = 28) and nondiabetic (*n* = 67) patients

	Nondiabetic	Diabetic	Total	Person $\chi^2(3)$ LLR $\chi^2(3)$
Sex				
Female	11	4	15	–
Male	56	24	80	0.79
Marital status				
Single	51	17	68	–
Married	6	6	12	–
Divorced	8	5	13	0.19
Widow	2	0	2	–
Job				
Jobless	51	18	69	–
Professional	1	0	1	0.30
Retired	15	10	25	–
Education				
Illiterate	15	7	22	–
Low grade	38	15	53	0.99
High grade	12	5	17	–
University	2	1	3	–
Socioeconomic status				
Very low	18	8	26	0.40
Low	44	16	60	–
Moderate	5	3	8	–
Highly moderate	0	1	1	–

LLR, likelihood ratio.

Table 5 Clinical characters of diabetic (*n* = 28) and nondiabetic (*n* = 67) patients

	Nondiabetic	Diabetic	Total	Person $\chi^2(3)$ LLR $\chi^2(3)$
Symptom at onset				
Negative	2	1	3	–
Positive	49	23	72	–
Mixed	16	4	20	0.56
Schizophrenia subtypes				
Residual	10	4	14	–
Undifferentiated	28	13	41	–
Paranoid	16	6	22	–
Disorganized	8	2	10	0.64
Schizoaffective	5	3	8	–
Family psychiatric history				
Negative	37	10	47	–
Positive	30	18	48	0.83
Family medical history				
Negative	46	19	65	–
Positive	21	9	30	0.93

LLR, likelihood ratio.

Discussion

Patients with schizophrenia are at high risk for physical comorbidities such as metabolic dysregulation and CVD, leading to increased mortality (Phelan *et al.*, 2001; Lawrence *et al.*, 2003; Thakore, 2005).

In the current study the prevalence of definite cases of MS according to the International Diabetes Federation criteria 2004 was 23.15% and that for high risk was 49.4%. Those at risk represented 17.8% of cases.

The prevalence rate observed in this study is commensurate with the general prevalence of 10–22% found in the study by Ford *et al.* (2002) and almost similar to the prevalence found in the study by Straker *et al.* (2005) (29.2%) but lower than that in the studies by Correll *et al.* (2007) (47%) and Heiskanen *et al.* (2003) (37%) and significantly different from the 52.5% found in a similar study conducted on chronic, long-stay hospital patients with schizophrenia (El-Tayebani, 2007).

The wide variation between the current and other studies could mainly be because of different methodological diagnostic criteria defining MS, such as in the study by El-Tayebani (2007), who studied a similar sample depending mainly on American Medical Association (2001) and WHO 1999 in which lipid, sugar, and blood pressure levels are cardinal. Hence, cases that did not undergo treatment for metabolic dysregulations based on control of diet and lifestyle measures were included, besides excluding patients at risk who fulfilled only one or two criteria. This was not the case in the current study, in which only cases undergoing treatment for diabetes mellitus, hypertension, and dyslipidemia were included. Variability could also be explained by cultural differences and genetic predispositions; for example, USA has a higher prevalence of obesity and MS than does the UK (Ford *et al.*, 2002).

However, the overall risk for MS in the current study was very high; 90.6% of patients had either a degree of variable risk or actual MS.

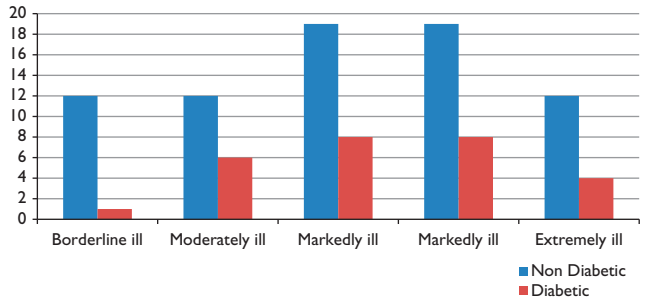
The higher risk of MS in this study may have been because of one or more risk factors, such as schizophrenia itself,

Table 6 Age, clinical data, and mini mental state examination scores of diabetic (*n* = 28) and nondiabetic (*n* = 67) patients

	Nondiabetic	Diabetic	Total	Person $\chi^2(3)$ LLR $\chi^2(3)$
Age (years)	48.07 ± 10.5	50.2 ± 9.8	48.9 ± 10.3	0.35
Age at onset (years)	22.8 ± 4.9	20.5 ± 5.8	21.2 ± 5.7	0.06
Duration of illness (years)	27.3 ± 9.2	27.6 ± 9.5	27.5 ± 9.3	0.89
Number of relapses	19.2 ± 12.7	19.0 ± 12.5	19.07 ± 12.5	0.93
Relapse duration (months)	4.1 ± 6.7	3.09 ± 1.8	3.3 ± 3.9	0.44
Last stay duration (years)	10.5 ± 6.6	9.5 ± 6.1	9.8 ± 6.2	0.47
Total stay duration (years)	14.8 ± 6.8	14.6 ± 7.7	14.6 ± 7.4	0.88
MMSE score	20.8 ± 6.8	18.9 ± 7.2	19.4 ± 7.1	0.24

LLR, likelihood ratio; MMSE, mini mental state examination.

Figure 2



Illness severity CGI scores among diabetic ($n=28$) and nondiabetic ($n=67$) patients with chronic schizophrenia ($P=0.43$). Note: the higher the CGIS score, the more severe the illness ($P=0.43$).

Table 7 Current treatment characteristics of diabetic ($n=28$) and nondiabetic ($n=67$) patients

	Nondiabetic	Diabetic	Total	Person $\chi^2(3)$ LLR $\chi^2(3)$
Current treatment category				
Conventional	18	5	23	–
Atypical	49	23	72	0.35
Treatment number				
Monotherapy	56	24	80	–
Polytherapy	11	4	15	0.79
Treatment dosage				
≥1000 mg cpz equivalent	62	25	87	–
<1000 mg cpz equivalent	5	3	8	0.86
Current differential drug types				
Clozapine	26	11	37	–
Resperidone	13	7	20	–
Olanzapine	5	4	9	–
Quitiapine	6	0	6	–
Aripiprazole	1	0	1	0.30
Haldol	14	4	18	–
Sulpride	2	1	3	–
Pimozide	1	1	2	–

Cpz, chlorpromazine; LLR, likelihood ratio.

chronicity, long duration of hospital stay, antipsychotic treatments, anthropometric characteristics, medical state (obesity and metabolic dysregulations), sociodemographics, clinical characteristics, and finally lifestyle or complex interactions for all of the above-mentioned risks.

Schizophrenia as a risk factor

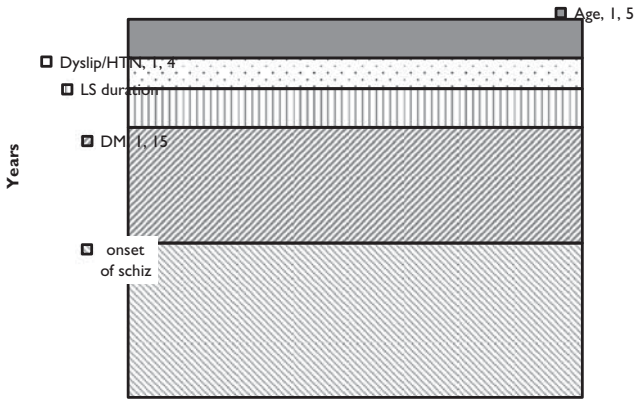
Heiskanen *et al.* (2003) found that the frequency of MS was two to four times higher in a group of people with schizophrenia, treated with typical and atypical neuroleptics, than in an appropriate reference population. This could be explained by the disease itself, wherein unaffected first-degree relatives of people with schizophrenia have high rates of type 2 diabetes mellitus (19–30%), pointing toward a genetic predisposition toward both illnesses (Mukherjee *et al.*, 1989). Further, over 15% of drug-naive individuals with first-episode schizophrenia have impaired fasting glucose levels, hyperinsulinemia, and high levels of the stress hormone cortisol (Ryan *et al.*, 2003).

Table 8 Medical illness and physical state among diabetic ($n=28$) and nondiabetic ($n=67$) patients

	Nondiabetic	Diabetic	Total	Person $\chi^2(3)$ LLR $\chi^2(3)$
Hypertension				
Negative	56	10	66	–
Positive	11	18	29	0.000**
Dyslipidemia				
Negative	43	6	49	0.000**
Positive	24	22	46	–
BMI				
≥30	29	20	49	–
25–29.9	24	5	29	0.04*
<25	14	3	17	–
Waist circumference (cm)				
≥102 male ≥88 female	31	19	50	–
94–101.9 male 84–87.9 female	16	3	19	0.13
<94 male <84 female	20	6	26	–

LLR, likelihood ratio.
*Significant if $P<0.05$.
**Highly significant if $P<0.001$.

Figure 3



Median values of age, onset of schizophrenia, last stay duration (LS), onset of diabetes mellitus, hypertension and dyslipidemia in years.

Schizophrenia is a long-standing stress factor with hypercortisolemia due to hypothalamic pituitary adrenal axis overactivity or defective feedback leading to obesity and metabolic changes. Hence, high risk of MS such as in melancholic depression and Cushing syndrome is associated with physical illness related to hypercortisolemia (Thakore, 2001; Ryan *et al.*, 2004). In addition, schizophrenia may increase the predisposition to MS by exacerbating and potentiating other risk factors such as sedentary life, poor dietary habits, limited access to care, and antipsychotic drug-induced adverse effects (Narasimhan and Raynor, 2010).

In our study the role of schizophrenia itself is unclear because unfortunately there is no control group having other similar psychiatric disorders to be compared against and prove the illness itself as risk. Also, the median time to onset of diabetes, hypertension, and dyslipidemia in our case is far from the age at onset of schizophrenia

Table 9 Predictive value and diagnostic accuracy for individual criteria of metabolic syndrome in chronic patients with schizophrenia

Criterion	Sensitivity	Specificity	PPV	NPV	DA
BMI ≥ 25	77.53	100	100	23.08	78.95
Male waist circumference (cutoff point ≥ 101 cm)	68.52	84.62	90.24	56.41	73.75
Diabetes mellitus	100.00	38.81	40.58	100.00	56.84
Hypertension	93.1	36.36	39.13	92.31	53.68
Dyslipidemia	86.96	40.82	57.97	76.92	63.16

DA, diagnostic accuracy; NPV, negative predictive value; PPV, positive predictive value.

(15, 24, and 24 years, respectively) and thus lack the temporary relation to the major constituents of MS.

Chronicity

The current results indicate that aging, longer duration of illness, and chronic course are significantly associated with both risky cases and definite cases for MS.

This may be understandable in the context of the suggestive finding of one or more risk factors for chronic MS, such as diabetes mellitus, hypertension, and dyslipidemia. This is also supported by results indicating a higher incidence of diabetes mellitus with age; Wild *et al.* (2004) concluded that the most important demographic change across the world in relation to diabetes prevalence appears to be an increase in the proportion of people aged 65 years and above. Further Al Kalaf *et al.* (2010) reported that age was the first significant independent predictor for the incidence of diabetes mellitus in a sample of Kuwaiti people. The dependency of the prevalence of MS on age is seen in most populations around the world (Anthony, 2008).

Chronic institutionalization

In our sample there was no significant association between risk of MS and long hospital stay or total stay period ($P = 0.77$ and 0.16) despite the fact that risky and definite cases for MS were distributed among patients with long duration of hospital stay. The lack of significance may indicate that chronic institutionalization may not be a powerful risk factor in our study in which controlled diet, smoking restriction, and sport activity helped to eliminate risk. This is supported by the results of Sugawara *et al.* (2011), in which higher prevalence of MS was seen in outpatients (48.1%) than in inpatients (15.8%) pointing to the importance of monitoring and minimizing the risk associated with changing lifestyles.

Antipsychotic medications

The relation of antipsychotic medication to type 2 diabetes and MS is unclear. In the present study we cannot ignore the effect of antipsychotic drugs on metabolic dysregulations and high prevalence of risks for MS despite a lack of significant association with either current medications or drugs at onset, as well as with various previous drug trails to treat MS and diabetes mellitus. Similar results were observed in Heiskanen *et al.* (2003), Cohn *et al.* (2004), and Straker *et al.* (2005).

This could be explained by the fact that most of our patients had repeated admissions, which was mainly because of noncompliance to treatment. The only period when compliance was obtained was during the last long hospital stay, in which adjusted environments may have decreased the risk of antipsychotic medication. Furthermore, with chronicity, the environmental factors can overcome the effect of drugs on weight gain, which predisposes diabetes mellitus and MS (Zipursky *et al.*, 2005).

Reports on the incidence of diabetes mellitus and metabolic dysregulation on drug-naive and first-episode schizophrenia have been documented in Ryan *et al.* (2003).

Obesity

Central obesity is a key feature of MS, reflecting the fact that its prevalence is driven by a strong relationship between WC and increased adiposity (BMI). However, despite the importance of obesity, patients of normal weight may also be insulin resistant and may suffer from MS (Anthony, 2008). Ryan and Thakore (2002) highlighted the potential role of visceral fat in cancer, cardiovascular illness, type 2 diabetes, and dyslipidemia. This was related to antipsychotic drugs (American Diabetic Association 2004) or may be independent of drugs and possibly due to HPA axis dysfunction (Rosmond and Björntorp, 2000). It was also reported to be present in drug-naive patients three times more than in the matched group (Thakore *et al.*, 2002).

In the current study there was a highly significant relationship between BMI and WC, indicating an association of general adiposity and visceral obesity with increased risk and definite cases of MS. Presence of type 2 diabetes was also significantly associated with BMI ($P = 0.04$) but not with WC ($P = 0.13$).

The value of BMI compared with WC in detecting the relative risk for diabetes mellitus and MS is under debate. Vazquez *et al.* (2007) demonstrated that BMI, WC, and waist/hip ratio have a similar association with incident diabetes. This was replicated by Ho *et al.* 2001, but Wang *et al.* (2007) reported that BMI was as reliable as or better than WC in predicting lipid risk and cardiometabolic factor. In contrast, Denke *et al.* (1994) indicated the importance of WC for detecting risk of cardiometabolic illness independent of BMI.

Our results indicate that BMI (cutoff point ≥ 25) has the highest sensitivity and predictive value as well as DA in detecting risk for MS, which may show the importance of this simple measure for detecting risk. However, WC of greater than or equal to 84 was powerful for detecting MS in women, as all studied women ($n = 15$) with schizophrenia lay in the high-risk ($n = 11$) and definite MS group ($n = 4$).

The lack of data about cutoff points for WC in the Mediterranean and Middle East (Arab) region, where the study was conducted, led to confusion in determining male and female scores. IDF 2004 recommends at least 94 cm for men and at least 80 cm for women, whereas El-Tayebani, (2007) used the cutoff point of at least 102 cm for men and at least 89 cm for women. Al Khalaf *et al.* (2010) used the same criteria, with both studies utilizing the NCEP and American Heart Association/updated NCEP guidelines (Grundy *et al.*, 2004). Using different cutoff points led to different results.

The current results concluded that BMI of at least 25 and WC of at least 94 for men and of at least 84 for women can detect the substantial risk of MS in the Arab culture, whereas cutoff points for BMI of at least 30 and for WC of at least 102 for men and of at least 88 for women can detect actual cases with definite MS.

Metabolic dysregulation

Diabetes, hypertension, and dyslipidemia were highly associated with MS ($P = 0.000$). Diabetes mellitus was also highly associated with hypertension and dyslipidemia ($P = 0.000$). Moreover, the sensitivity and NPV of these factors in relation to MS were high, but with modest specificity and DA. These results are commensurate with those of El-Tayebani (2007).

From the above data we can conclude that regularly monitoring simple measures such as BMI, WC, blood sugar, lipid profile, and blood pressure in patients with chronic schizophrenia is highly helpful for avoiding cardiometabolic risk.

Sociodemographics and clinical characters

There was no significant association between sociodemographics and schizophrenia characteristics in patients with diabetes mellitus in this study, nor for MS. Regarding gender, women were found to have high risk and actual MS ($P=0.01$), however, men were highly represented in both groups. This is consistent with the results of Sugawara *et al.* (2011).

Interestingly, patients with high negative scores on PANSS had lower risk for MS. This is consistent with a significant inverse association of total negative score with BMI ($P = 0.002$, $r = -0.319$) and higher negative PANSS scores in nondiabetic cases (30.3 ± 10.6 for negative cases versus 24.8 ± 10.9 for positive cases with diabetes mellitus, $P = 0.03$).

The weak predictive value of clinical and sociodemographics for MS in our findings was also documented by Heiskanen *et al.*, 2003. This may indicate that the risk for metabolic dysregulation is complex and is an outcome of the interaction between multiple factors such as centeral obesity and insulin resistance (Nakamura *et al.*, 1994; Bonora *et al.*, 1998; Anderson *et al.*, 2001; Nesto, 2003; Carr *et al.*, 2004).

Lifestyle predisposition

According to the WHO, Ministry of Health in Kuwait (2007) and 2005, which studied the Kuwaiti general population, Kuwaiti men within the age group of 40–60 years (matched with our patient age group) had the following risk factors: 23.2% were smokers (10–20 cigarettes/day); 42.1% had significantly reduced physical activity; 41.1% had hypertension; 19.7% were diabetic; 78.8% had WC of at least 93 cm; 50.5% had total cholesterol level of at least 5.2 mmol/l; 9.8% had a high cholesterol level of at least 6.5 mmol/l; and finally 50.5% of them had three or more of the above risk factors.

This means that Kuwaiti men are highly vulnerable to cardiometabolic risks, which may have a role in the ethnic predisposition toward such a problem (WHO, Ministry of Health in Kuwait, 2007 and 2005). The study on ethnic and cultural predisposition for cardiometabolic risk is quite important and needed in future research.

Conclusion and recommendation

(1) The risk of MS is high among patients with chronic schizophrenia, which mandates careful monitoring and elimination of risk factors.
(2) BMI and WC as well as blood sugar and lipid profile are considered simple measures for detecting risk factors.
(3) Studying cardiovascular risk, which is very important for patients with chronic schizophrenia with high mortality due to natural causes, is mandatory for highly vulnerable patients.

Limitations

(1) For the diagnosis of MS, the current study depended on actually treated cases of metabolic dysregulation, which may have disregarded cases with disturbed biochemistry dependent on diet and lifestyle management.
(2) Absence of a control group comprising the general population or other matched groups may limit the generalization of data.

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Conflicts of interest

There are no conflicts of interest.

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