Prevalence of Metabolic Syndrome in Schizophrenic Patients

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Abstract

Metabolic syndrome (MS) & other cardiovascular risk factors are highly prevalent in schizophrenic patients. Patients are at risk for premature mortality & overall have limited access to physical health care. To date there have been scarce studies that provide estimates of MS in schizophrenic patients in Iraq.

The aim of the study is to examine the prevalence of MS & related factors in schizophrenic patients.

By using a case-control design we recruited100 patients out of 118 with the DSM-IV diagnosis of schizophrenia who were attending outpatient department of Al-Diwaniya Teaching Hospital during the period between1st March to 15th December 2013,. The MS prevalence was assessed based on National Cholesterol Education Program Adult Treatment Panel III criteria. Comparative analysis was performed between patients & 100 participants as representative of general population.

the study revealed that the overall prevalence of MS in schizophrenic patients was (27%). It is significantly higher with obesity, smoking, family history of obesity. Waist circumference, low High Density Lipoprotein & raised blood pressure showing a significant difference between both groups. The anti-psychotic medication having a high association with metabolic syndrome is Olanzapine.

Schizophrenic patients on antipsychotic medications had high prevalence of MS compared to the general population & this emphasize the need for regular monitoring of various metabolic parameters in patients on antipsychotics.

انتشار متلازمة الايض عند مرضى الفصام

الخلاصة

متلازمة الايض وعوامل الخطر القلبية والوعائية سائدة في مرضى الفصام. هؤلاء المرضى عرضة للوفاة المبكرة ولديهم إمكانية محدودة للحصول على الرعاية الصحية.إن الدراسات حول معدل انتشار متلازمة الايض في العراق قليلة جدا. ألأهداف: هو دراسة انتشار متلازمة الايض والعوامل ذات العلاقة في مرضى الفصام.

تم دراسة 100 مريض من أصل 118مصاب بالفصام حسب تشخيص دي أس أم الرابع في مستشفى الديوانية التعليمي أثناء الفترة بين الأول من آذار إلى الخامس عشر من كانون الأول 2013،وبدراسة مقارنة.تم تقييم انتشار متلازمة الايض استنادا على برنامج تعليم الكولوستيرولِ الوطنيِ.تم التحليل المقارن إحصائيا بين مرضى الفصام و100 مشارك كممثل من عامة الناس.

كشفت الدراسةَ بأن انتشار متلازمة الايض في مرضى الفصام كانَ27 %. وهي أعلى عند الذين لديهم سمنة، تدخين، تأريخ عائلي من السمنة. محيط خصر، بروتين الدهن الثقيل (إتش دي إل)، وارتفاع ضغط الدم وكلها ذات دلاله إحصائية هامة. الاولانزابين الدواء المضاد للذهان له ارتباط عالي بمتلازمة الايض.

أكثر من عامة الناس. وهذا يؤكد الحاجة للمراقبة الايض مرضى الفصام الذين يتناولون الأدوية المضادة للذهان كانوا يعانون من متلازمة الايض في المرضى الذين يتناولون الأدوية المضادة للذهان. المنتظمة لمتلازمة.

Introduction

Metabolic syndrome (MS), first described by Reaven in 1988, reflects a clustering of classical cardiovascular risk factors including insulin resistance, central obesity, elevated blood pressure, high triglyceride level & low levels of high density

lipoprotein, these associated risk factor have been previously called syndrome X or insulin resistance syndrome [1]. Although insulin resistance is believed to be the key pathogenetic factor of the MS [2,3], the pathogenesis underlying the clustering of cardiovascular risk factors remain unclear : genetic, obesity, & inflammation have been suggested to be involved [4,5].

Five definitions for the MS have been developed by The National Cholesterol Education Programme (NCEP) 2001[6] & NCEP 2004 [7].The World Health Organization(WHO) [8].The International Diabetes Federation (IDF) [9] & The European Group for Study of Insulin Resistance (EGIR)[10].All definitions includes measure of blood pressure, triglycerides, HDL cholesterol &fasting glucose level. The NCEP Adult Treatment panel III criteria (ATPIII) are superior in term of simplicity, requiring fasting glucose assessment instead of oral glucose tolerance test

The NCEP criteria include the following parameters:

Abdominal obesity (waist circumference)	
Men	> 102 cm (40 in)
Women	> 88 cm (35 in)
Triglyceride	≥ 150 mg/dl (1.7 mmol/L)
High density lipoprotein cholesterol (HDL-c)	
Men	< 40 mg/dl (1.0 mmol/L)
Women	< 50 mg/dl (1.3 mmol/L)
Blood pressure	
Systole	≥ 130 mm Hg
Diastole	≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dl (≥ 6.1 mmol/L)

The MS is diagnosed when 3 or more of the above features are present.

Individuals with the NCEP-defined MS have a 65% increased risk for cardiovascular disease compared to those without the syndrome, and the risk increases 93% if the WHO definition is used[11].In Europeans, the presence of the MS was associated with an approximate twofold increased risk for incident cardiovascular morbidity & mortality[12].

Risk Factors:

Stress:

Recent research indicates prolonged stress can be an underlying cause of MS by upsetting the hormonal balance of the hypothalamic-pituitary-adrenal axis (HPA-axis)[13].A dysfunctional HPA-axis causes high cortisol levels to circulate, which results in raising glucose and insulin levels, which in turn cause insulin-mediated effects on adipose tissue ,ultimately promoting visceral adiposity, insulin resistance, dyslipidemia and hypertension [14].Psychosocial stress is also linked to heart disease [15].

Central Obesity:

Central obesity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity. [16].

Sedentary lifestyle:

Physical inactivity is a predictor of cardiovascular diseases (CVD) events. Many components of MS are associated with a sedentary lifestyle, including increased adipose tissue , reduced HDL cholesterol; & a trend toward increased triglycerides, blood pressure, & glucose in the genetically susceptible. [17].

Aging:

MS affects 44% of the US population older than age 50. With respect to that demographic, the percentage of women having the syndrome is higher than that of men. The age dependency of the syndrome's prevalence is seen in most populations around the world [18].

Diabetes Mellitus Type 2:
An estimated 75% of British patients with type 2 diabetes or impaired glucose tolerance (IGT) have MS. The presence of MS in these populations is associated with a higher prevalence of CVD than found in patients with type 2 diabetes or IGT without the syndrome [19].

Coronary Heart Disease:
The approximate prevalence of the MS in patients with coronary heart disease (CHD) is 50%, with a prevalence of 37% in patients with premature coronary artery disease (age 45), particularly in women.[20]

Schizophrenia and Other Psychiatric Illnesses:
Patients with schizophrenia may have a predisposition to MS that is exacerbated by sedentary lifestyle, poor dietary habits, possible limited access to care, and antipsychotic drug-induced adverse effects. [21]

Rheumatic Diseases:
There are new findings regarding the comorbidity associated with rheumatic diseases. Both psoriasis & psoriatic arthritis have been found to be associated with MS [22].

Mechanisms Underlying Metabolic Syndrome in Schizophrenia:
The putative mechanisms linking atypical antipsychotic medications to MS are multifactorial, and likely include the interplay of dopamine, histamine, orexigenic (anabolic) neuropeptides, adrenergic and muscarinic receptors, and failed glucose homeostasis, as well as the interaction of these with modifiable and non-modifiable risk factors [23]. On a clinically relevant level, weight gain has been a well-known side effect of atypical antipsychotic medications, though references to excessive weight gain exist for first-generation antipsychotic agents, as well. Sedentary lifestyle & other risk factors, such as smoking & poor diet, may be contributory; however atypical antipsychotic agents induce changes in weight that are primarily responsible for changes in glucose metabolism [24,25].

Aims of The Study
To investigate the prevalence of MS and related factors in schizophrenic patients.

Material and Methods
The study included patients fulfilling the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR diagnostic criteria for schizophrenia.
A case-control study was performed. Out of 118 schizophrenic patients who were screened, 100 patients gave their consent &came back for fasting blood investigations & full MS profile.
A face-to-face interview with schizophrenic patients on antipsychotic medications in outpatient department/Al-Diwaniya Teaching Hospital was conducted during the period between1st March-15th December2013. The participant information sheets clearly stated that declining to take part would not influence their clinical treatment.
Data on socio-demographic variables & current antipsychotic medications were collected. Height, weight, sitting blood pressure and waist circumference were measured. All patients were informed to fast for a minimum of 8 hours prior to this study visit. A fasting blood sample was taken for fasting blood sugar & fasting lipid profile.
MS prevalence was estimated using the criteria of the National Cholesterol Education Program (NCEP), the 2001 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Treatment Panel III (ATP III) assessing the presence of three or more of the following components: abdominal obesity (waist circumference $\geq$ 90cm in males and $\geq$ 80 cm in females), hyper triglyceridemia (fasting triglyceride concentration $\geq$ 150 mg/dL), dyslipidemia (fasting HDL cholesterol: <40 mg/dL in men;<50 mg/dL in women), hypertension, (systolic/ diastolic blood pressure $\geq$ 130/85 mm Hg), and hyper-glycemia (fasting glucose concentration $\geq$ 100 mg/dL).

Laboratory tests:
Blood tests include: fasting lipid profile:[total cholesterol (TC), high density lipoprotein (HDL-c), low density lipoproteins (LDL-c) and triglycerides (TG)] , & fasting glucose.

Inclusion Criteria:
1. Schizophrenic patients on antipsychotic drugs for at least one year.
2. Patients age above 15 years old.

Exclusion Criteria:
1-Any patient who did not have capacity to provide informed consent.
2-Patients receiving mood stabilizer.
3-Patients receiving combination of antipsychotic drug and mood stabilizer
4-Schizophrenic patients taking medications for metabolic abnormalities.

Statistical Analysis:
All statistical analyses were conducted using Statistical Package for Social Sciences SPSS. The conventional 5% significance level was used throughout the study. Continuous variables were tested using the t-test non-parametric test. Frequency of categorical variables were tested using chi-square tests. P-value of < 0.05 was considered statistically significant.

Results:

The results are shown in the following tables and figures:

Age Distribution: The mean age of the patients was 46.4 ± 15.2 & for controls 45.7 ±16.8 years .No significant difference was found between cases & controls P>0.05.

Table 1: Age distribution of schizophrenic patients and controls

Age (year)	Cases (N=100)		Controls (N=100)	
	No.	%	No.	%
15- 25	7	7.0	10	10.0
26-35	32	32.0	28	28.0
36-46	33	33.0	35	35.0
47-56	21	21.0	18	18.0
57-66	7	7.0	9	9.0
Total	100	100.0	100	100.0
Mean		46.4 ± 15.2		45.7 ± 16.8

P. value = 0.37

Gender Distribution: Among cases females were 53 (53%) & males were 47 (47%) compared to 55 (55%) & 45 (45%) among controls, respectively. (Fig.1)

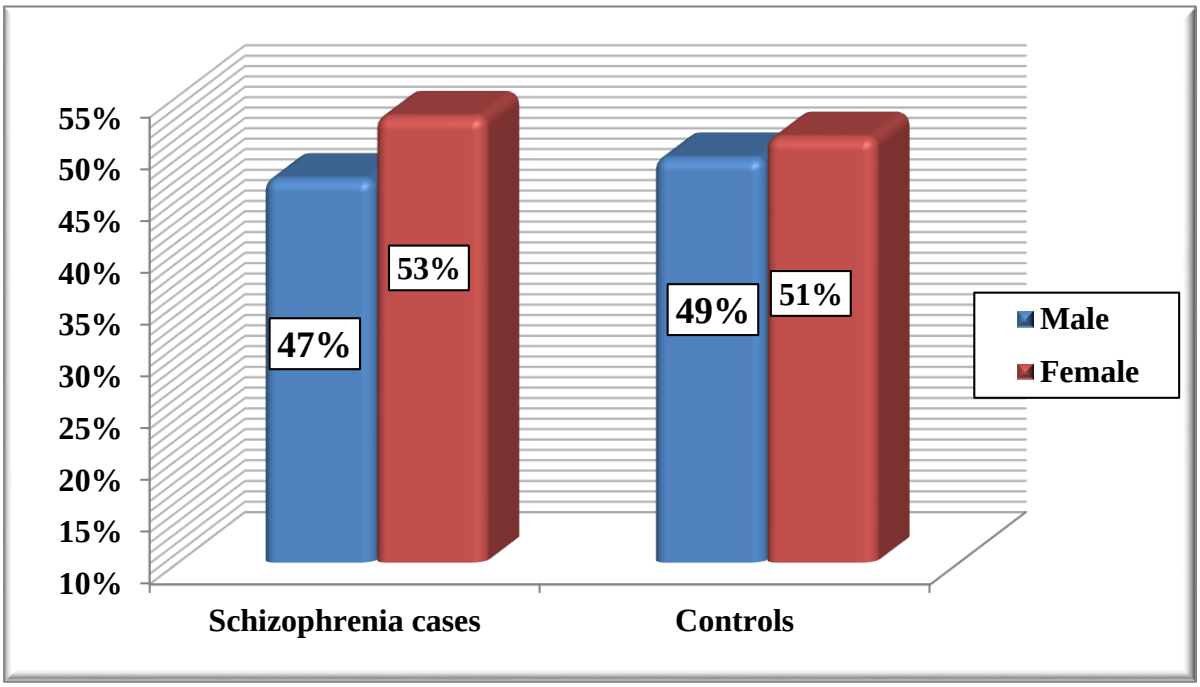

Figure 1: Gender distribution of studied groups

BMI Distribution: (3%) of cases & (4%) of controls were underweight (BMI <18). Overweight represents 20% of cases and 43% of controls, the three categories of obesity represent 36% of cases and 20% of controls. There was a statistically significant difference in BMI between study groups; cases were more likely to be more overweight than controls, the mean BMI of cases was significantly higher than that of controls; 29.6 ± 4.6 vs. 26.8 ± 4.2, (P= 0.035).

Table 2: BMI distribution (mean and categories)

BMI categories (kg/m^2)	Cases		Control		P. value
	No.	%	No.	%	
Underweight(<18)	3	3.0	4	4.0	0.011
Normal(18-24.9)	20	20.0	43	43.0	
Overweight (25-29.9)	41	41.0	33	33.0	
Obesity I (≥ 30)	18	18.0	12	12.0	
Obesity II (35 – 39.9)	12	12.0	5	5.0	
Obesity III (≥ 40)	6	6.0	3	3.0	
Total	100	100.0	100	100.0	
Mean BMI (kg/m^2)	29.6 ± 4.6		26.8 ± 4.2		0.001

Level of Education Distribution: No significant difference between cases and controls, concerning distribution of the level of education P > 0.05.

Table 3: Frequency distribution of level of education of studied groups:

Level of education	Cases (No.=100)		Control(No.=100)	
	No.	%	No.	%
Illiterate	25	25.0	22	22
Primary	35	35.0	38	38.0
Secondary	20	20.0	21	21.0
Higher	20	20.0	17	17.0
Total	100	100.0	100	100.0

Types and Period of Physical Activity: Walking was the predominant physical activity type in both cases and controls, representing 65% & 69% respectively, followed by domestic activity in 22% of cases& 19% of controls, riding a bicycle in 6% of cases & 5% of controls, playing football in 6 % of the cases and 7% of the controls & the least experienced physical activity was lifting weight 1%. No significant difference had been found between cases and controls in physical activity &the duration of physical activities, P>0.05.

Table 4. Frequency distribution of types & period of physical activity:

Variable	Cases		Control		P. value
	No.	%	No.	%	
Physical activity					
Walking	65	65.0	69	69.0	0.62
Domestic activity	22	22.0	19	19.0	
Riding a bicycle	6	6.0	5	5.0	
Playing football	6	6.0	7	7.0	
Lifting weight	1	1.0	0	0.0	
Total	100	100.0	100	100.0	
Time of physical activity/week					
0 -2 hours	19	19.0	15	15.0	0.66
2-5 hours	27	27.0	29	29.0	
5-7 hours	25	25.0	31	31.0	
7-10 hours	16	16.0	17	17.0	
10 or more/week	13	13.0	8	8.0	
Total	100	100.0	100	100.0	

Smoking Habit: 64% of cases &28% of controls were current smokers, 10% & 13% were former smokers, and 26% , 59% were non-smokers among cases and controls, respectively. There was a statistically significant association between current smoking and cases, P=0.01.

Table 5: Distribution of smoking habits:

Smoking habit	Cases		Controls	
	No.	%	No.	%
Current smoker	64	64.0	28	28.0
Former smoker	10	10.0	13	13.0
Non-smoker	26	26.0	59	59.0
Total	100	100.0	100	100.0
P. value = 0.001				

Family History: Positive family history of diabetes or hypertension was not significantly different between cases & controls, P >0.05.Positive family history of obesity was significantly associated with schizophrenia. Cases were more likely to have positive family history of obesity than controls; 31% vs. 24% respectively, P=0.002.

Table 6: Distribution of family history of chronic diseases & obesity:

Family history		Cases (N=100)		Control(N=100)		P. value
		No.	%	No.	%	
Diabetes	Yes	25	25.0	27	27.0	0.67
	No	32	32.0	35	35.0	
	Don't know	43	43.0	48	48.0	
Hypertension	Yes	23	23.0	18	18.0	0.15
	No	32	32.0	47	47.0	
	Don't know	45	45.0	39	39.0	
Obesity	Yes	31	31.0	24	24.0	0.002
	No	22	22.0	41	41.0	
	Don't know	47	47.0	35	35.0	

Duration of schizophrenia: Among cases the duration was < 3 years in 15%, 3-6 years in 23%, 7-10 years in 25% and >10 years in 37% of cases.

Table 7: Distribution of duration of disease of schizophrenic cases:

Duration (years)	No.	%
< 3	15	15.0
3 – 6	23	23.0
7 - 10	25	25.0
> 10	37	37.0
Total	100	100.0

Components of MS: According NCEP ATP III criteria, risky waist (>102 cm in males and > 88 in females) was present in 65% of cases and 49% of controls, it had been significantly found that schizophrenic cases were about 2 folds more likely to have risky waist than controls (OR = 1.93, 95%CI [1.1 – 3.4], P=0.032).

Low HDL level (< 40 mg/dl in males & < 50 mg in females) was significantly more frequent among cases than controls, 29% vs. 9% respectively, (OR=3.68, 95%CI[1.6-8.3], P=0.002).

Raised blood pressure (≥130/≥ 85) mmHg was more frequent among cases; representing 3 folds more than controls (OR=2.7, 95 % CI [1.12-6.5], P=0.022).

The other 2 components of MS; Hyperglycemia (≥ 100 mg/dl) and triglycerides ≥ 150 mg/dl, showed no statistically significant differences between cases and controls, P>0.05.

Table 8: Distribution of component of MS according to NCEP ATP III:

MS component	Cases (N=100)		Control(N=100)		OR (95% CI)	P. value
	No.	%	No.	%		
Risky waist > 102 cm in males > 88 cm in females	65	65.0	49	49.0	1.93 (1.1 – 3.4)	0.032
Hyperglycemia (≥ 100 mg/dl)	23	23.0	18	18.0	1.36 (0.8 – 2.33)	0.70
Low HDL < 40 mg/dl in males < 50 mg/dl in females	29	29.0	9	9.0	3.68 (1.6-8.3)	0.002
Triglycerides ≥ 150 mg/dl	22	22.0	16	16.0	1.48 (0.73 – 3)	0.36
Raised blood pressure (≥130/≥85) mmHg	19	19.0	8	8.0	2.7 (1.12 – 6.5)	0.022

OR (95% CI); odds ration & 95% confidence interval

Combination of MS criteria: 14% of cases had 3 criteria of MS, 9% has 4 criteria & 4% of cases had all 5 criteria, those cases that had 3 or more criteria were 27%. Among controls those who had 3 criteria were 8%, 4 criteria in 3% and 5 criteria 1%, in total those control who had 3 or more of the MS criteria were12%. The difference between cases and control regarding the combination of MS criteria was statistically significant.

Table 9: Distribution of collected criteria of MS:

No. of criteria of MS	Cases (N=100)		Control (N=100)	
	No.	%		
0	22	22.0	36	36.0
1	27	27.0	30	30.0
2	24	24.0	21	21.0
3	14	14.0	8	8.0
4	9	9.0	3	3.0
5	4	4.0	1	1.0
Total	100	100.0	100	100.
P. value = 0.006				

According to the findings in tables 8 and 9 the prevalence of MS was 27% among cases and 12% among controls. Fig. 2.

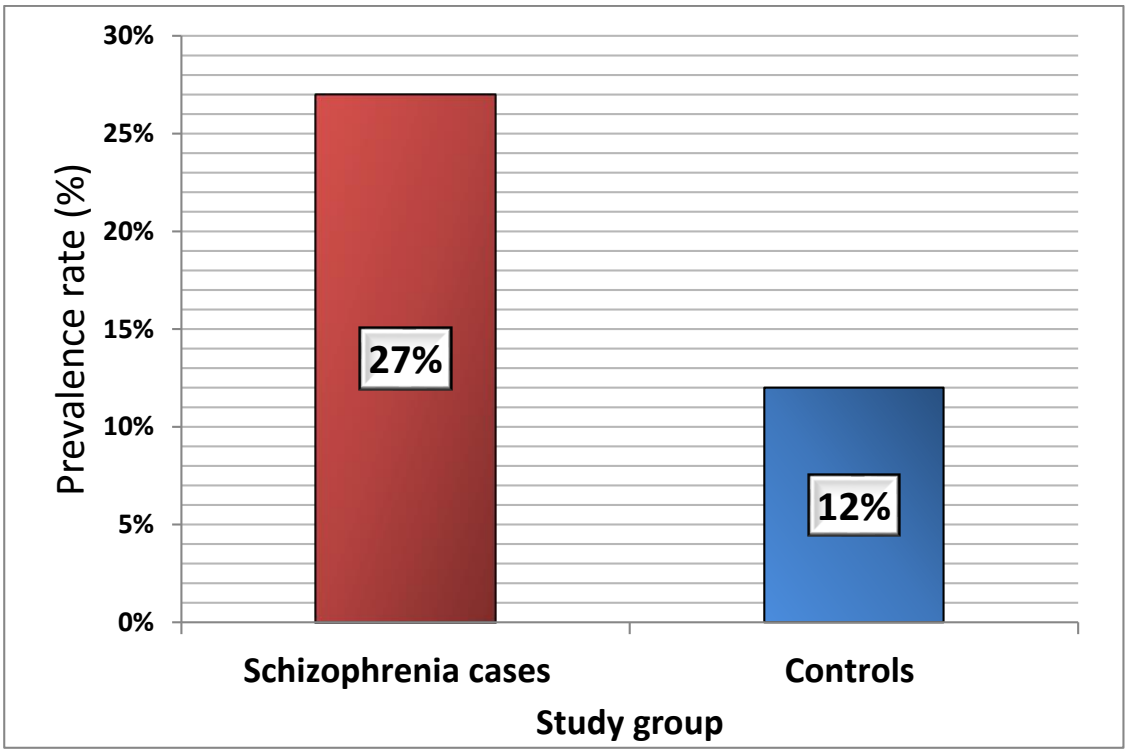

Figure 2: Prevalence of MS among studied group

MS & gender: No significant difference had been found in the prevalence of MS between both genders in both studied group, P>0.05.

Table 10: Gender distribution of 39 participants with MS:

No. of criteria of MS	Cases (N=27)		Controls (N=12)	
	No	%	No.	%
Male	11	11.0	5	5.0
Female	16	16.	7	7.0
Total	27	27.0	12	12.0
P. value = 0.78				

MS and Antipsychotic Medications: Olanzapine {second generation antipsychotics (SGA)} was the more frequent medication used among schizophrenic patients, it was used by 46% of patients. It had been significantly found that MS was more prevalent among cases who used this medication for 3-4 years which represents 71.4% of this group, P=0.031.

Resperidone (SGA) was the second more frequently used medication; used by 34% of cases, 17.6% of them had MS and the association was statistically not significant, P>0.05

First generation antipsychotics (FGA): MS was found in 15% of the 20 cases who used these medication & there was no significant association between the MS & the use of these medications, P>0.05.

Table 11: MS and antipsychotic medications:

Medication	Duration of medication (year)	Frequency	MS (No. (%)	P value
Olanzapine	1 - 2	18	5 (27.8)	0.031
	3 – 4	14	10 (71.4)	
	5 -6	10	2 (20.0)	
	≥ 7	4	1 (25.0)	
Total		46	18 (33.9)	
Resperidone	1 - 2	15	1 (6.7)	0.48
	3 – 4	11	3 (27.3)	
	5 -6	5	1 (20.0)	
	≥ 7	3	1 (33.3)	
Total		34	6 (17.6)	
First generation antipsychotics	1 - 2	6	1 (16.7)	0.71
	3 – 4	9	1 (11.1)	
	5 -6	3	1 (33.3)	
	≥ 7	2	0 (0.0)	
Total		20	3 (15.0)	

Discussion:

There have been scarce studies that provide estimates of MS in schizophrenic patients in Iraq. The prevalence of MS was 27% among cases and 12% among controls This result is consistent with other studies done by Cem CERİT et al, Fuminari Misawa, Rezaei O et al and M De Hert who showed that the prevalence of MS was (21%, 22.2%, 27.4%, and 28.4% respectively) [26,27,28,29]. This result is lower than that of Hatata H.& Karoline Krane-Gartiser studies in which the prevalence of MS were 38.09% &41,1% respectively [30,31].These differences could be explained by ethnical & genetic differences between different populations that were studied or due to differences in methodology. The increased rate of MS can be explained by bad lifestyle factors that commonly seen in mentally ill patients such as physical inactivity, poor dietary habits, smoking & drinking [32]

There was no statistically significant differences in the prevalence of MS regarding age, gender, level of education, types & period of physical activity between the two groups.

The prevalence of MS in women was higher than in men, but the difference was not statistically significant. This is in concordance with Rezaei O and [28] Cem CERİT studies [26]. Rezaei O explained this higher rate in female simply due to their higher visceral fat & central obesity [26].

We found a positive correlation for MS with the groups of Olanzapine as main medications with statistically significant value, especially for those who are on the medication for 3-4 years. Resperidone was the second more frequently used medication but the association was statistically not significant.

We found no statistically significant correlation between MS &FGA which is similar to another study conducted in this perspective which found that MS was more prevalent in patients with longer duration of drug intake especially Olanzepine ,Risperidone [30].

The current smokers were more frequent in schizophrenic patients than controls & there was significant association & this is inconsistent with other studies [26,30].

The study revealed that there is no statistically significant association between MS & positive family history of DM, & HT. This finding indicates that other environmental or acquired factors have more influence in the development of MS than genetic factors & this is in agreement with other studies [30,31].

Positive family history of obesity was significantly associated with schizophrenia. Cases were more likely to have positive family history of obesity than controls. Mean WC was higher in MS group than control group with a statistically significant difference .The increased WC in MS group of patients was inconsistent with previous studies [5, ,33].

Low high density lipoprotein, raised blood pressure was significantly more frequent among cases than controls. While the other 2 components of MS; Hyperglycemia & triglycerides, showed no statistically significant differences between cases & controls.

Longer duration of diagnosis with schizophrenia is associated with more prevalent MS. This goes with the Cem CERİT study stating that illness & treatment durations of patients with MS were longer than in patients without MS [26]. This relation was not significant in the Hatata H, study [30]. M De Hert, study confirmed that MS significantly increases with increased duration of illness. This might be related to the combined effects of illness & drug treatment on metabolic problems (e.g. weight gain & high blood pressure) or the length of illness/treatment duration might have been directly linked to increased age [26] .

Our study should be interpreted within the context of the following limitations: First we enrolled subjects with stable schizophrenia state while acutely ill & more chronically sedentary patients were not included which affects the generalization of

the results. Second this study lacks the power to examine combinations of different antipsychotic medications. Third this study does not check quantity & quality of patient's food intake, which is contributing to the patient's health state and relating to the metabolic problems. We can conclude that the prevalence of MS in schizophrenic patients receiving antipsychotics was high. Our data adds to the mounting evidence that schizophrenic patients treated with SGA are at increased risk for developing MS.

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