Metabolic Syndrome in Patients With Schizophrenia

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Background: Our aim was to study the frequency of metabolic syndrome and associated factors in patients with schizophrenia.

Method: The study group consisted of 35 outpatients with long-term schizophrenia defined by DSM-IV criteria. Patients were assessed for the presence of metabolic syndrome, which was defined by the criteria of the National Cholesterol Education Program. All patients were on antipsychotic medication. Data were collected from Jan. 1, 2001, to Aug. 30, 2001.

Results: Metabolic syndrome was found in 37% (N = 13) of the patients, and it was associated inversely with the total daily dose of, but not with any specific type of, antipsychotic drug.

Conclusion: The results suggest that metabolic syndrome is common among patients with schizophrenia, and it may be far more common than in general populations.

(J Clin Psychiatry 2003;64:575–579)

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Patients with schizophrenia who are in their forties have a life expectancy 6 to 7 years lower than that of general population subjects,[1] which is not entirely explained by unnatural deaths. A recent Finnish study suggested that men with schizophrenia may have an elevated risk of cardiovascular death.[2]

During the last several years, there has been growing interest in the metabolic side effects associated with antipsychotic medication, such as weight gain,[3–5] increased serum levels of triglycerides,[6–10] decreased high-density lipoprotein (HDL) cholesterol levels,[11,12] and increase in circulating insulin levels.[13] These side effects have been associated with the use of both conventional and novel antipsychotics.

Type 2 diabetes mellitus is more common among people with schizophrenia than in general populations.[14] In case reports, new-onset diabetes mellitus has been described following the use of both clozapine and olanzapine.[15] Two recent studies have suggested that there are differences between antipsychotics with respect to the risk of diabetes mellitus.[16,17] A study consisting of a large group of patients with schizophrenia found that the prevalence of diabetes mellitus was significantly increased among patients who received clozapine, olanzapine, and quetiapine, but not among those receiving risperidone.[16] A population-based study from Great Britain suggested that there is a higher risk of diabetes associated with olanzapine than risperidone.[17] In a long-term follow-up study of patients treated with clozapine, the development of diabetes was predicted by age but did not associate with other factors such as initial body mass index or body weight changes or increased levels of triglyceride or cholesterol.[10]

The metabolic syndrome, also known as insulin resistance syndrome, is an enigmatic disorder that includes 5 major features: (1) disturbed glucose metabolism and/or (2) disturbed insulin metabolism (impaired glucose tolerance or type 2 diabetes mellitus or insulin resistance, hyperinsulinemia), (3) obesity (particularly abdominal fat distribution), (4) dyslipidemia (hypertriglyceridemia or decreased HDL cholesterol), and (5) hypertension.[18]

Other factors associated with metabolic syndrome are hyperphagia, increased dietary fat content, smoking, low physical activity level, blood clotting abnormalities, altered adipose tissue physiology, sex hormone abnormalities, altered pituitary adrenal function, and difficulty in coping with stress.[19,20] However, the pathogenesis of this syndrome remains unclear, although environmental factors such as diet and physical inactivity coupled with as yet largely unknown genetic factors clearly interact to produce the syndrome.[18,21,22]

Metabolic syndrome can be considered as an established risk factor for type 2 diabetes mellitus and cardiovascular diseases.[23] It also increases mortality from cardiovascular diseases from all causes.[24] A large Finnish and Swedish study[25] found that subjects with metabolic syndrome had a 3-fold increased risk of coronary heart disease and stroke.

The prevalence of metabolic syndrome has varied from 10% to 22%.[26–28] Vanhala and coworkers[29] have reported that the prevalence of metabolic syndrome was 8% in women and 17% in men in a sample of the Finnish gen-

eral population. Nevertheless, different criteria for metabolic syndrome have been used in these studies, and only Vanhala et al. used an unselected sample in their study. Recently, in a population-based study, the frequency of metabolic syndrome was assessed from a cohort of 1038 men from the same area as those in the present study.[30] In that large cohort, metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP), was present in 11% of men, and this criterion had high specificity (0.89) in predicting the development of type 2 diabetes during the follow-up. In women, the frequency of metabolic syndrome has been assessed in a cross-sectional population-based study[31] conducted in an area close to that of the present study, using other criteria. In women, the frequency of metabolic syndrome according to looser criteria was 19.5% (106/543), and 6.3% (34/543) met the standards of the more strict criteria. In that study, the looser criteria were defined as fulfillment of 3 of the 8 criteria for metabolic syndrome.

Studies of patients with schizophrenia have so far focused mainly on individual components of metabolic syndrome; we found no reports concerning the frequency of metabolic syndrome and associated factors. However, as several single components of the metabolic syndrome have been found to be quite common among patients with schizophrenia, our main hypothesis was that the frequency of metabolic syndrome might also be high. Furthermore, we studied the associated factors of metabolic syndrome in patients with schizophrenia.

METHOD

The study group consisted of 35 patients with schizophrenia or schizoaffective disorder consecutively discharged between April 1, 1997, and Dec. 21, 1998, from the psychiatric rehabilitation ward at Kuopio University Hospital in eastern Finland. The study was approved by the local Ethical Committee of Kuopio University Hospital and the University of Kuopio. All patients gave written informed consent to participate. Data were collected from Jan. 1, 2001, to Aug. 30, 2001. Diagnoses according to DSM-IV criteria[32] were confirmed from patient case records by 2 independent psychiatrists. Of the initial patient group (N = 60), 3 had died after discharge as a result of suicide, aspiration, and alcohol and drug intoxication; all except the suicide victim were drunk at the time of death. Thirty-six patients initially agreed to participate in the study, but 1 patient withdrew. During the study period, all 35 subjects (19 men and 16 women) in the final sample were outpatients.

The 22 patients who refused to complete the study were younger than the study subjects (mean [SD]

Table 1. Characteristics of Treatment With Antipsychotic Medication in Patients With Long-Term Schizophrenia in Relation to the Presence of Metabolic Syndrome

Variable	Metabolic Syndrome: Yes (N = 13)	Metabolic Syndrome: No (N = 22)	p Value
Chlorpromazine equivalents, mg/d			
Mean (SD)	505.3 (157.7)	681.8 (292.9)	.04
Range	250–700	300–1300	
No. of antipsychotics			
Mean (SD)	1.3 (0.5)	1.7 (0.6)	.08
Range	1–2	1–3	
Duration of novel antipsychotic use, y			
Mean (SD)	7.0 (4.1)	5.0 (4.1)	.16
Range	2.7–12.8	1.5–16.6	
Total no. of medications			
Mean (SD)	5.5 (2.5)	4.0 (2.5)	.10
Range	1–11	1–10	
No. of drugs used when required			
Mean (SD)	1.5 (1.3)	0.7 (1.2)	.02
Range	0–4	0–5	
Antipsychotics, N			
Clozapine	7	14	.72
Olanzapine	3	4	
Conventional	3	4	

Table 2. Demographic and Clinical Characteristics of 35 Outpatients With Long-Term Schizophrenia in Relation to the Presence of Metabolic Syndrome

Variable	Metabolic Syndrome: Yes (N = 13)	Metabolic Syndrome: No (N = 22)	p Value
Age, y			
Mean (SD)	48.8 (7.6)	42.0 (11.2)	.10
Range	37.4– 60.8	24.9–59.0	
Age at onset of schizophrenia, y			
Mean (SD)	28.3 (8.1)	26.5 (5.5)	.68
Range	17.9–40.4	19.3–36.8	
Duration of schizophrenia, y			
Mean (SD)	20.5 (14.3)	15.5 (11.8)	.37
Range	3.3–39.4	3.4–39.6	
Service utilization			
Hospital days			
Mean (SD)	3137 (3278.1)	2029 (2325.8)	.75
Range	586–10226	319–9385	
No. of hospital treatment sessions			
Mean (SD)	28 (26.8)	16 (12.4)	.38
Range	8–99	3–54	
Time since the last discharge, mo			
Mean (SD)	24.2 (11.4)	24.8 (13.1)	.79
Range	1.2–40.3	0.8–45.5	
SAPS score			
Mean (SD)	1.3 (1.1)	1.2 (0.9)	.99
Range	0–4.0	0–2.8	
SANS score			
Mean (SD)	2.3 (0.9)	2.5 (0.8)	.44
Range	1–4.2	1.2–3.8	
Calgary Depression Scale score			
Mean (SD)	3.5 (4.0)	3.9 (3.8)	.78
Range	0–12	0–13	
Simpson-Angus Scale score			
Mean (SD)	0.7 (0.4)	0.7 (0.6)	.62
Range	0.2–1.6	0.1–2.2	
GAF score			
Mean (SD)	34.8 (7.1)	35.5 (5.7)	.74
Range	21–50	22–45	

Abbreviations: GAF = Global Assessment of Functioning, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

Table 3. Components of Metabolic Syndrome in 35 Patients With Schizophrenia

Variable	Metabolic Syndrome: Yes (N = 13)	Metabolic Syndrome: No (N = 22)	p Value
BMI (kg/m^2)			
Mean (SD)	30.8 (4.0)	26.0 (4.0)	.004
Range	26.8–37.3	19.5–34.3	
HDL cholesterol, mmol/L			
Mean (SD)	0.93 (0.40)	1.37 (0.40)	.006
Range	0.59–1.78	0.78–2.10	
Triglycerides, mmol/L			
Mean (SD)	3.10 (2.15)	1.15 (0.42)	.001
Range	0.95–7.40	0.59–1.90	
Fasting blood glucose, mmol/L			
Mean (SD)	6.7 (1.5)	5.3 (1.5)	< .001
Range	5.1–10.5	4.4–6.4	
HbA_{1c}, %			
Mean (SD)	6.2 (0.6)	5.6 (0.4)	.002
Range	5.3–7.3	4.8–6.4	
Insulin, mU/L			
Mean (SD)	17.1 (10.0)	9.3 (5.3)	.06
Range	6.7–37.6	4.4–25.0	
Waist girth, cm			
Mean (SD)	112 (11)	93 (10)	< .001
Range	100–131	77–107	
Systolic blood pressure, mm Hg			
Mean (SD)	134 (12.7)	120 (12.5)	< .001
Range	115–153	99–144	
Diastolic blood pressure, mm Hg			
Mean (SD)	83 (11)	79 (9)	.14
Range	67–104	67–98	

Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein.

age = 37.4 [10.9] vs. 45.0 [10.4] years, p = .01), and in line with this they also had fewer hospital days (mean [SD] = 1052 [989] vs. 2356 [2475] days, respectively; p = .02). Nevertheless, there was no difference in gender distribution between those who did not complete the study and the study subjects (59% men vs. 54% men, respectively; p = .72).

Metabolic syndrome was diagnosed according to the criteria of the NCEP.[20] The metabolic syndrome was defined by the NCEP criteria as the presence of 3 or more of the following: fasting blood glucose levels ≥ 5.6 mmol/L, serum triglycerides ≥ 1.7 mmol/L, serum HDL cholesterol < 1.0 mmol/L in men and < 1.2 mmol/L in women, blood pressure ≥ 135/85 mm Hg or on medication, and waist girth > 100 cm or > 88 cm for men and women, respectively.

One patient in the sample had drug treatment for both dyslipidemia and diabetes, and 2 others had medication for diabetes. Nevertheless, all of these patients fulfilled the NCEP criteria for metabolic syndrome, and therefore the medications used did not affect the results.

Clinical measurements were conducted by patients' own general practitioners or their nurses in municipal health centers. Height and body weight were measured with the patients in light underwear and without shoes. Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Blood pressure was recorded as the mean of 2 or 3 measurements after 10 to 15 minutes of rest in the sitting position. Blood samples were taken after 12 hours of fasting. Blood glucose was measured twice if the first result was > 5.6 mmol/L, and the mean was used in subsequent analysis. The current use of drugs was registered from patient files and verified by the nursing staff. Psychotic symptoms were assessed with the Scale for the Assessment of Positive Symptoms[33] and the Scale for the Assessment of Negative Symptoms.[33] Psychosocial symptoms were assessed with the Global Assessment of Functioning[32]; depressive symptoms, with the Calgary Depression Scale[34]; and extrapyramidal symptoms, with the Simpson-Angus Scale.[35]

The significance of differences in proportions was determined with the chi-square test, and differences between means were assessed using the Student t test or Mann-Whitney U test, depending on the data distribution.

RESULTS

The frequency of metabolic syndrome diagnosed according to NCEP criteria was 37% (N = 13) in our cohort of patients with long-term schizophrenia. Nine men (47%) and 4 women (25%) had metabolic syndrome (p = .17). Metabolic syndrome associated inversely with the daily dose of antipsychotic drugs and positively with the number of drugs used when required (Table 1). There was no association between the presence of metabolic syndrome and any other antipsychotic drug or other medication-related factors. Over half of the study group used clozapine. Nevertheless, there was no difference in mean daily dose between clozapine users with and without metabolic syndrome (mean [SD] dose = 483 [157] mg vs. 503 [164] mg, p = .80). No significant differences were found between the groups in sociodemography or clinical variables (Table 2).

The prevalences of different components of metabolic syndrome in the sample were as follows: fasting blood glucose level ≥ 5.6 mmol/L, 46% (16/35); serum triglyceride ≥ 1.7 mmol/L, 31% (11/35); serum HDL cholesterol < 1.0 mmol/L (in men), 58% (11/19) and < 1.2 mmol/L (in women), 25% (4/16); blood pressure ≥ 135/85 mm Hg or on medication, 26% (9/35); and waist girth > 100 cm (in men), 68% (13/19) and > 88 cm (in women), 75% (12/16). As expected, the patients with metabolic syndrome differed from the others in all of the individual features of metabolic syndrome except diastolic blood pressure (Table 3).

DISCUSSION

In this sample of long-term outpatients with schizophrenia, the frequency of metabolic syndrome was 2- to

4-fold higher than has been previously found in the same geographical area in both men (47% vs. 11%–17%) and women (25% vs. 6%–20%).[29–31] In comparing these prevalence rates, it must be noticed that Vanhala et al.[29] used different criteria for metabolic syndrome than we used. Laaksonen et al.,[30] however, used in a large population-based sample the same criteria that were used in our study. Findings from Laaksonen et al.[30] and Korhonen et al.[31] indirectly but strongly support a conclusion that metabolic syndrome is more common among patients with schizophrenia than in the general population. This is in accordance with a recent review suggesting that metabolic syndrome is likely to be common in schizophrenia.[36]

A further possibility for the overrepresentation of metabolic syndrome is that antipsychotic drugs induce single components of metabolic syndrome.[5,7,9,10,15] We did not find associations between metabolic syndrome and different types of antipsychotic drugs or the estimated duration of antipsychotic use. Interestingly, the mean dose of antipsychotic drugs measured as chlorpromazine equivalents was lower but the number of drugs used was higher in the metabolic syndrome group. As a whole, antipsychotic medication is a single, and possibly indirect, factor in the consideration of many factors associated with metabolic syndrome in patients with schizophrenia. Nevertheless, the fact that most patients used clozapine limits generalization of our findings.

Finally, some recent studies suggest that low birth weight is a common risk factor for both schizophrenia and metabolic syndrome.[37,38] This suggestion also raises the question of whether common risk factors partly explain the high frequency of metabolic syndrome in patients with schizophrenia.

Limitations of the present study are its relatively small sample size and lack of a control group, and therefore our findings are to be considered as suggestive. However, the alarmingly high frequency of metabolic syndrome in this sample warrants further studies of the prevalence and risk factors in patients with schizophrenia. If future studies confirm these findings, they would highlight the need for treatment and preventive programs targeting general health in patients with schizophrenia. Recently, it has been shown that currently recommended levels of physical activity protect markedly from the development of metabolic syndrome, even after extensive adjustment for potential mediating and confounding factors, especially in men at high risk for the development of metabolic syndrome.[39] This finding could also be applicable to psychiatric patients, and promoting physical activity among them might have marked overall health benefits in this patient group. It is worth remembering that patients with schizophrenia often have limitations in keeping their physical health and identifying their physical illnesses without help from mental health care and primary care providers.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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