Archives of Psychiatry and Psychotherapy, 2013; 2 : 15–20

Risk of metabolic syndrome in patients with schizophrenia: comparative study with population of bank employees in Russia

Ivan Martynikhin, Dmitry Tanyanskiy, Oxana Rotar, Vladislav Solntsev, Nina Sokolian, Nikolay Neznanov, Alexandra Konradi, Eugene Shlyakhto, Alexander Denisenko.

Summary

Aim. This study is dedicated to evaluation of the prevalence of metabolic syndrome and its components in patients with schizophrenia in Russia.
Methods. 138 patients with schizophrenia who received antipsychotic medication and 138 mental healthy subjects from 1,561 bank employees cohort matched to schizophrenic patients by sex, age and body mass index were enrolled to the study. Fasting blood plasma levels of glucose, lipids, insulin, cortisol, prolactin concentrations were determined.
Results. In comparison with control group, patients had significantly higher frequency of metabolic syndrome and abdominal type of obesity (according to NCEP ATP III and IDF criteria). In spite of lesser level of plasma glucose and total cholesterol, plasma insulin and triglycerides concentrations were higher in patients with schizophrenia. High density lipoprotein cholesterol concentration was lower in patients while arterial blood pressure level didn't differ between groups. Cortisol and prolactin levels were elevated in the patient group, but these hormones neither correlated with metabolic syndrome nor with any metabolic parameters studied.
Discussion. The study conducted in Russia revealed the increased frequency of metabolic syndrome in schizophrenic patients in comparison with mental healthy cohort. The main disorders found in the patient group were abdominal obesity, insulin resistance and dyslipidemia.
Conclusion. Results obtained in this study should be taken into account when developing of medical treatment of patients with schizophrenia.

schizophrenia / antipshychotics / metabolic syndrome / obesity / insulin resistance

Ivan Martynikhin[1], Dmitry Tanyanskiy[2], Oxana Rotar[3], Vladislav Solntsev[3], Nina Sokolian[1], Nikolay Neznanov[1], Alexandra Konradi[3], Eugene Shlyakhto[3], Alexander Denisenko[2]. [1]St.-Petersburg I.P. Pavlov State Medical University, Department of Psychiatry and Narcology, [2]Institute of Experimental Medicine, Russian Academy of Medical Sciences; [3]Almazov Federal Heart, Blood and Endocrinology Center, St. Petersburg. Correspondence address: dmitry.athero@gmail.com

Part of this study was supported by the state contract no. 06/303 from 30.05.2008 of the Ministry of Science and Education of Russian Federation (Program "Prevention of socially important diseases" (2007–2011), section "Diabetes Mellitus"). The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

INTRODUCTION

In comparison with general population, mortality among patients with schizophrenia is 2-3 times higher [1, 2] and life expectancy is 20-25 % lower [3]. In addition to high incidence of suicides, the cited studies revealed high cardiovascular and type 2 diabetes associated mortality of schizophrenic patients [1, 2]. One of the main reasons of elevated cardiovascular and type 2 diabetes risks in patients with schizophrenia can

be the high prevalence of obesity and metabolic syndrome among that people. Thus, according to studies conducted in USA, Canada and several Western European countries, frequency of metabolic syndrome (MS) in schizophrenic patients is 1.5-2 times higher than in general population or mental healthy people [4-8].

Recent investigation of 1,561 bank employees in Russia, St. Petersburg revealed that MS frequency in studied population is 21.5% according to IDF criteria and 18.8%, according to ATP2005 [9]. These data are corresponding well to the prevalence of MS in USA and Western Europe [4, 5]. Meanwhile the prevalence of MS among patients with schizophrenia in Russia has been never assessed. Therefore the present study was performed in order to compare pairwise MS frequencies between patients with schizophrenia, examined in one of the St. Petersburg mental hospitals, with mental healthy people from the above mentioned bank employees cohort.

METHODS

181 patients with diagnosis of schizophrenia (ICD-10) were enrolled among those who live in one of the districts of St. Petersburg. 12 patients refused from the examination, 5 were excluded because of uncertainty of schizophrenia diagnosis according to ICD-10, and data from one female were also excluded because she suffered from severe type 1 diabetes mellitus. As a result for matching protocol (see below) we included data from 163 patients (81 males and 82 females). All selected patients received antipsychotic drugs, and 49.7% of them – atypical antipsychotics (clozapine, olanzapine, risperidone). Written informed consent was obtained from all patients, and the Institutional Review Board of the V.M. Bechterev's St. Petersburg Psychoneurological Research Institute approved this study.

Arterial blood pressure, height, weight, and waist circumference were measured. Body mass index (BMI) was calculated according to Kettle's formula: BMI (kg/m^2) = weight (kg)/height^2 (m^2). Patients were fasted for 12 h before the venous blood was collected for determination of laboratory parameters and plasma glucose, total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglycerides levels were measured.

Controls were obtained from bank employee's cohort, which included 1,561 subjects [9]. As described, all subjects had been examined for the same anthropometrical parameters as in schizophrenia group, and at the fasting state in the morning their venous blood was drawn. For the pairwise comparison, we randomly selected every subject from the bank employee's cohort, matched by gender, age (±1 year) and BMI (±0.5 kg/m^2) to every examined patient with schizophrenia. When few people from the bank group had the same parameters as the patient, only one of them was chosen to the pair in a random way. In the case of absence of appropriate pair to the patient, the subject was excluded from the analysis.

The level of low density lipoprotein cholesterol (LDL-C, mmol/l) was calculated using the Friedewald formula: LDL-C = Total cholesterol – (triglycerides/2.2 + HDL-C). The cholesterol atherogenicity coefficient (AC) was calculated by the formula: AC = (total cholesterol – HDL-C)/ HDL-C. After measurement of glucose and lipid parameters plasma samples of both groups stored at –20 C and then some of them used for ELISA determination of insulin ("DRG Diagnostics" ELISA kit, Germany"), prolactin and cortisol ("Vector-best", Russia) concentrations. Insulin resistance HOMA index was assessed as follows: HOMA index = insulin (μIU/ml)* glucose (mmol/l) / 22.5. Metabolic syndrome was diagnosed according to NCEP ATP III [10] and IDF [11] criteria.

In statistical analysis we applied for the absolute parameters (e.g. concentrations) Student's t-test for dependent groups ("SPSS 17.0", IBM Corporation), for the relative parameters (e.g. %) McNemar's test in the case of dependent groups and Fisher's exact test in the case of independent groups (online calculator, GraphPad Software Inc., http://www.graphpad.com). For normalizing the data distribution some parameters were log transformed (see "Results"). The group differences were assumed to be statistically significant at p value less than 0.05.

RESULTS

While selecting a control group from bank employees we found 138 subjects well matched with schizophrenic patients according to match-

ing protocol (see methods). Clinical and metabolic characteristics of the selected groups are presented in Tab. 1.

As expected according to the selection criteria, groups did not differ in sex distribution, age and BMI. At the same time patients with schizophrenia had higher waist circumference than control group, what can indicate that schizophrenic patients are prone to abdominal redistribution of adipose tissue. In spite of a slightly lower glucose concentration, patient group was characterized by about 1.5 times elevation of plasma insulin levels and as a result – higher HOMA insulin resistance index in comparison with controls. Triglycerides level in patients with schizophrenia was increased, and HDL cholesterol was decreased, what is highly specific for MS. Surprisingly, serum levels of total and LDL cholesterol were also lower than in control group. However, 1.5 times decline of HDL-C levels in the patient group was more significant than a slight decrease of LDL and total cholesterol levels. As a result the value of cholesterol atherogenic coefficient was higher in schizophrenic patients than in control group. At the same time level of diastolic but not systolic arterial blood pressure was slightly decreased in the patient group (Tab. 1).

Table 1. Clinical and metabolic characteristics of patients with schizophrenia and control subjects matched for sex, age and BMI (Mean ± SD)

Parameters	Schizophrenia	Control	P value
Sex (males/females)	66/72	66/72	N.S.
Age (years)	40.8 ± 1.0	40.6 ± 1.0	N.S.
BMI (kg/m^2)	24.4 ± 0.4	24.5 ± 0.3	N.S.
Waist circumference (sm)	89.4 ± 10.6	84.1 ± 10.9	<0.0001
Glucose (mmol/l)*	5.0 ± 0.9	5.3 ± 1.0	0.02
Insulin (μIU/ml)* [1]	13.6 ± 7.9	9.3 ± 7.9	<0.0001
HOMA index* [1]	3.2 ± 3.7	2.2 ± 2.1	<0.001
Total cholesterol (mmol/l)	4.8 ± 1.2	5.3 ± 1.2	0.0001
LDL cholesterol (mmol/l)	3.0 ± 1.0	3.3 ± 1.0	0.03
HDL cholesterol (mmol/l)	1.0 ± 0.2	1.5 ± 0.5	<0.0001
Triglycerides (mmol/l)*	1.6 ± 0.8	1.2 ± 1.0	<0.0001
Cholesterol atherogenicity coefficient*	3.8 ± 1.3	2.9 ± 1.6	<0.0001
Systolic BP (mmHg)	120.8 ± 14.8	123.2 ± 17.5	N.S.
Diastolic BP (mmHg)	76.6 ± 9.2	79.7 ± 12.0	<0.01
Prolactin (μIU/ml)* [2]	601.9 ± 625.5	280.2 ± 141.5	<0.01
Cortisol (nmol/l) [2]	819.3 ± 239.3	487.6 ± 161.8	0.0001

* Values were log transformed before statistical analysis.

[1] Serum insulin and HOMA index values were measured in 102 pairs

[2] Serum prolactin and cortisol levels were measured in 73 pairs

SD – standard deviation, N.S. – no significant differences (p > 0.05), BMI – body mass index, LDL – low density lipoprotein, HDL – high density lipoprotein, BP – blood pressure

We also evaluated whether such metabolic characteristics of schizophrenic patients affect the frequency of metabolic disorders. As expected from above results schizophrenic patients in comparison with controls were more burden with abdominal obesity (1.7 and 1.3 fold according to ATPIII and IDF criteria, respectively), hypertriglyceridemia (2.2 fold), low HDL-C blood level (3.2 fold) and the patients had significantly lesser frequency of hyperglycemia (2.1 and 1.7 fold according to ATPIII and IDF criteria, respectively) (Tab. 2 – *next page*). At the same time frequency of arterial hypertension didn't differ between both groups.

Thus, three of five metabolic syndrome components more often presented in the group of schizophrenia, and as it is shown in Fig. 1, this group is also characterized by more frequent occurrence of metabolic syndrome diagnosed by both ATPI-II NCEP (2.9 fold, P<0.0001) and IDF (1.9 fold, P=0.0003) criteria in comparison with control. The frequency of metabolic syndrome in patients with schizophrenia was higher in both genders (except men, according to IDF criteria). The gender difference in metabolic syndrome burden observed only in the schizophrenic group, with more frequent disease in females (Fig. 1 – *next page*).

In the patient group but not in controls frequency of metabolic syndrome increased with age, with significant group differences at the age of more than 40 years (Fig. 2 – *next page*).

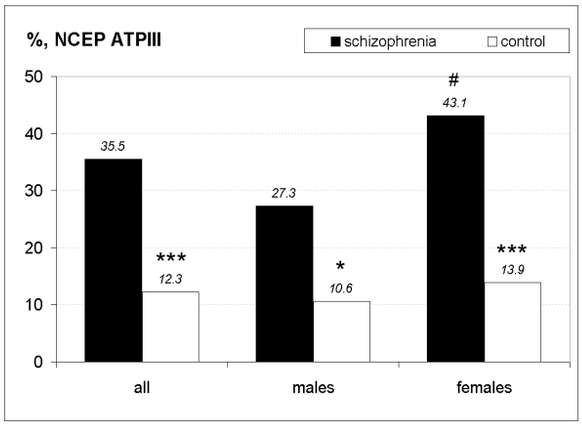
To evaluate whether metabolic differences between schizophrenic and control groups are explained by hormonal disturbances in patients with schizophrenia we compared the blood levels of prolactin and cortisol in both groups. As shown in Tab. 1, plasma prolactin and cortisol

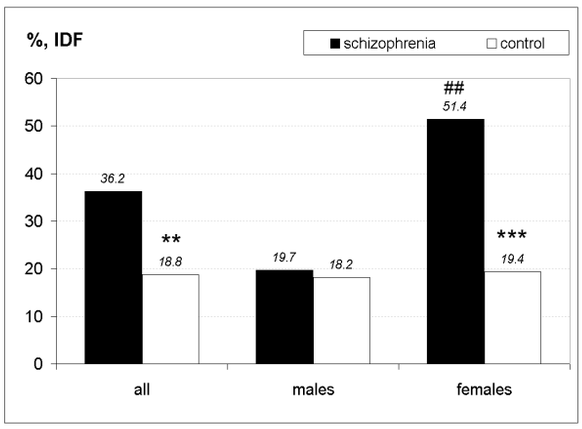
Table 2. Frequencies (%) of metabolic syndrome components estimated by NCEP ATP III (2001) and IDF (2005) criteria in patients with schizophrenia and in controls

MS components	Schizophrenia (n = 138)	Control (n=138)	P value
Abdominal obesity, ATP III	31.2	18.8	0.0005
Abdominal obesity, IDF	53.6	39.9	0.0023
Elevated triglycerides	32.6	14.5	0.0010
Declined HDL cholesterol	72.5	22.5	<0.0001
Elevated glucose, ATP III	8.7	18.1	0.0311
Elevated glucose, IDF	20.3	35.5	0.0117
Arterial hypertension	34.8	35.5	N.S.

MS – metabolic syndrome, HDL – high density lipoprotein, N.S. – no significant differences (p > 0.05)

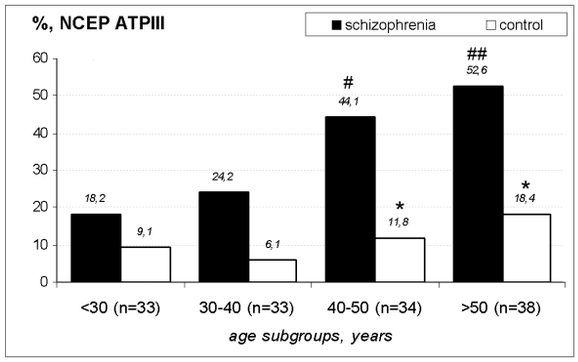
Fig 1. Frequency of metabolic syndrome according to NCEP ATPIII and IDF criteria in patients with schizophrenia and control subjects





* – statistical significant difference of metabolic syndrome frequency between schizophrenia and control groups at p< 0.05, ** – at p < 0.001,
*** – at p < 0.0001. – statistical significant difference of metabolic syndrome frequency between genders at p < 0,05, ## – at p < 0.0001

Fig 2. Frequency of metabolic syndrome according to NCEP ATPIII criteria in patients with schizophrenia and controls in different age subgroups



* – statistical significant difference of metabolic syndrome frequency between schizophrenia and control groups at p< 0.01. # – statistical significant difference of metabolic syndrome frequency in comparison with the first subgroup at p < 0.05, ## – at p < 0.01.

levels were about 2 times higher in the schizophrenic group, but were unrelated to MS, insulin, glucose and lipid parameters in both control and schizophrenia groups (data not shown).

DISCUSSION

Our investigation revealed that after matching for sex, age and BMI, in comparison with control bank employees group, patients with schizophrenia had significantly higher frequency of MS and some of its symptoms. Obtained results are in accordance with similar observations in studies conducted in the USA, Canada and some countries in Western Europe [4-8]. At the same time difference of MS frequency between schizophrenia and control groups in our study was only significant among subjects aged more than 40 years. Possibly, duration of schizophrenia, which increases with aging, has an important role in development of MS manifestations. But according to our previous observations [12], duration of schizophrenia *per se* (independent of age) had no impact on development of MS. Besides, in the group of schizophrenia, but not among the controls, MS was more prevalent in females. Thus, according to our study the presence of schizophrenia has a greater contribution on development of MS in females than in males and especially in persons at the age above 40 years. Meanwhile, some studies had shown that

MS frequency increases in patients with schizophrenia independently of age and gender [4, 7, 8]. The reasons of such discrepancies between results of our and other studies are not currently known.

Interestingly that in spite of high frequency of MS, patient group had lower lever of diastolic BP, plasma glucose and total cholesterol. At the same time, because of higher level of insulin, triglycerides and lower HDL-C plasma content, the integral indices of insulin resistance and blood lipid atherogenicity were significantly higher in patients. Observed metabolic disorders in schizophrenic patients can be explained by treatment of those persons with antipsychotic drugs. It was shown that antipsychotic medication, especially treatment with atypical antipsychotics, such as clozapine and olanzapine, leads to weight gain, elevation of insulin and atherogenicity of plasma lipids [13-15]. Metabolic effects of such drugs are not fully explained by weight gain due to their antagonism to 5-hydroxitriptamine and H1 histamine receptors in brain [16]. Indeed, according to cell culture experiments, atypical antipsychotics decrease glucose uptake in skeletal myocytes [17] and adipocytes [18], stimulate hepatic glycogenolysis [19] and lipogenesis [20]. At the same time since all schizophrenic patients in our study received antipsychotic medication, it's difficult to evaluate the impact of this treatment on development of MS. Besides, some authors describe elevation of visceral adiposity and insulin resistance in first-episode schizophrenic patients, who haven't received earlier antipsychotic drug therapy [21]. It is well known that people with schizophrenia are especially prone to stress and depression disorders. Therefore, metabolic disorders in these subjects can also be due to hyperproduction of simpatico-adrenal hormones. As it is shown in Tab. 1, plasma cortisol concentration was elevated in schizophrenic patients. But the level of this hormone did not correlate with any metabolic parameters studied (data not shown). Thus, at any case, high cortisolemia cannot explain the development of metabolic disorders in patients with schizophrenia.

Our study has several limitations. First, due to cross-sectional design of our investigation we cannot assert in full confidence that schizophrenia or medical treatment of this disease is a causal factor of MS development. Second, the absence of drug naïve patients in our study makes no possibility to evaluate the association between metabolic syndrome and schizophrenia *per se*. Third, control subjects were selected from organized population cohort (bank employees) and it still remains an open question whether frequency of MS and its components differs between patients of schizophrenia and general population. Nevertheless, this study conducted in Russia revealed the increased frequency of metabolic syndrome in schizophrenic patients in comparison with mental healthy cohort. The main MS components observed in the patient group are abdominal obesity, insulin resistance and dyslipidemia. Future comparison studies of drug naïve patients will unveil the question about the impact of antipsychotic medication on development of metabolic disorders in patients with schizophrenia.

REFERENCES

1. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry. 2010; 196: 116–121.
2. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res. 2000; 45: 21–28.
3. Laursen TM. Life expectancy among persons with schizophrenia of bipolar affective disorder. Schizophr Res. 2011; 131: 101–104.
4. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res. 2005; 80: 19–2.
5. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287: 356–359.
6. Heiskanen T, Niskanen L, Lyytikainen, R, Saarinen PI, Hintikka J. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry. 2003; 64: 575–579.
7. Cohn T, Prud'homme D, Streiner D, Kameh H, Remington G. Characterizing Coronary Heart Disease Risk in Chronic Schizophrenia: High Prevalence of the Metabolic Syndrome. Can J Psychiatry. 2004; 49: 753–760.
8. De Hert M, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes, metabolic syn-

drome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clin Pract Epidemiol Ment Health. 2006; 2: 14.

9. Konradi AO, Rotar OP, Korostovtseva LS, Ivanenko VV, Solntcev VN, Anokhin SB, et al. Prevalence of metabolic syndrome components in a population of bank employees from St. Petersburg, Russia. Metab Syndr Relat Disord. 2011; 9: 337–343.
10. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486–2497.
11. The International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome [article online], 2006, http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf, website of the International Diabetes Federation.
12. Neznanov NG, Martynikhin IA, Sokolian NA, Tanyansky DA. Risk factors of metabolic syndrome in patients with schizophrenia. Psikhitscheskie rasstroistva v obstchei medicine (Mental disorders in general medicine). 2009; 3: 13–17.
13. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight-gain: a comprehensive research synthesis. Am J Psychiatry. 1999; 156: 1686–1696.
14. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents. Arch Gen Psychiatry. 2005; 62: 19–28.
15. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical and atypical antipsychotics. Am J Psychiatry. 2003; 160: 290–296.
16. Lean MEJ, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. Diabetes Care. 2003; 26: 1597–1605.
17. Ardizzone TD, Bradley RJ, Freeman AM, Dwyer DS. Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs rusperidone and clozapine, and structural analogs of clozapine. Brain Res. 2001; 923: 82–90.
18. Vestri HS, Maianu L, Moellering DR, Garvey WT. Atipical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. Neuropsychopharmacology. 2007; 32: 765–772.
19. Hampson LJ, Mackin P, Agius L. Stimulation of glycogen synthesis and inactivation of phosphorylase in hepatocytes by serotonergic mechanisms, and counter-regulation by atypical antipsychotic drugs. Diabetologia. 2007; 50: 1743–1751.
20. Oh KJ, Park J, Lee SY, Hwang I, Kim JB, Park TS, et al. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. Am J Physiol Endocrinol Metab. 2011; 300: 624–632.
21. Thakore JH. Metabolic disturbance in first-episode schizophrenia. Br J Psychiatry. 2004; 184 (Suppl. 47): 76–79.