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CLINICAL STUDY

Metabolic risk in selected second-generation antipsychotics

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Abstract: *Background:* Many studies have reported higher incidence of metabolic abnormalities in patients receiving antipsychotic medications than in general population.
Objectives: The objective of our study was to determine the prevalence of metabolic syndrome in a group of patients receiving long-lasting antipsychotic treatment and also whether the cardiovascular risk among different second-generation antipsychotics varies.
Methods: Our study group consisted of 71 patients who were on antipsychotic monotherapy for at least 12 months. In each patient, fasting plasma glucose, HDL cholesterol, triglycerides, liver enzymes, bilirubin and plasma immunoreactive insulin levels were examined. We measured body weight, height, body mass index, waist circumference and body fat percentage together with blood pressure and heart rate. We assessed metabolic syndrome prevalence in the study group and correlations among its components as well as between them and other variables. The data were processed by statistics programme STATISTICA 8.0. For detection of correlations Spearman's rank correlation test was used.
Results: The prevalence of metabolic syndrome in our sample reached 41 %. The highest prevalence rate of 50 % was detected in the olanzapine subgroup. Identical prevalence of 40 % was observed in quetiapine and risperidone subgroups. The lowest prevalence of 25 % and 31 % was observed in sertindol and amisulpirid subgroup, respectively. The prevalence rate of metabolic syndrome in men was 51 % compared to 34 % in women.
Conclusion: According to metabolic syndrome prevalence rates olanzapine appears to be associated with the highest cardiovascular risk, amisulpirid and sertindol appear to be much safer *(Tab. 2, Ref. 13)*. Full Text in free PDF *www.bmj.sk*.
Key words: antipsychotics, metabolic syndrome, cardiovascular risk.

Antipsychotics are psychotropics drugs which are widely used to treat a variety of psychiatric disorders. As a group they represent the foundation of treatment for psychotic disorders. The first antipsychotic – Chlorpromazine – was discovered in 1952 by the French psychiatrist Pierre Deniker. At the time, it was considered a miracle drug because it helped many people with schizophrenia to be able to live outside the institution for the first time. These medications are primarily indicated to treat acute exacerbations of schizophrenia as well as to prevent relapses. Their high efficacy has been confirmed in many other indications, including schizoaffective disorder, psychotic and treatment-resistant depressions, manic and mixed phases of bipolar disorder either as monotherapy or as adjuncts to mood stabilizers**.** Moreover, they are essential in treating irritability, restlessness, agitation, and also in managing qualitative disorders of consciousness associated either with severe acute somatic disorders or decompensated chronic somatic disorders. The development of the second-generation agents, also referred to as „atypicals", has brought two main advantages over formerly used conventional antipsychotic drugs. This class of medications is characterized by greater efficacy, especially in treating negative symptoms of schizophrenia as well as cognitive deficits. Another positive finding about the atypicals is that they carry significantly less risk of causing extrapyramidal side effects (1). Second generation antipsychotics have emerged as first-line drugs for treatment of psychotic disorders. As time goes on however, there continues to be growing concern about weight gain, metabolic syndrome and endocrine changes associated with their administration.

It is no surprise that the second-generation antipsychotics are associated with an elevated risk of metabolic syndrome as there have been numerous studies reporting higher incidence of metabolic abnormalities such as weight gain, increases in levels of plasma lipids, and new-onset type II diabetes mellitus in patients receiving antipsychotic medications than in general population (2–4). The metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes consisting of:

- central (abdominal) obesity,
- diabetes, IFG (impaired fasting glycaemia) and IGT (impaired glucose tolerance),
- hypertension,

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- dyslipidaemia (elevated triglyceride levels, low HDL cholesterol levels).

Each component of the metabolic syndrome is an established cardiovascular risk factor. Interestingly, the presence of multiple components represents greater risk than the summation of the risks associated with each individual factor (5). It is known that affected individuals suffer from two- to three-fold higher cardiovascular mortality rates and two-fold higher all-cause mortality rates (6). The significant two-fold increase in the risk of coronary heart disease and higher incidence of stroke or myocardial infarction in these patients makes this condition dangerous (7). Whether the risk of metabolic syndrome varies among the different second-generation antipsychotics remains unclear. That is why the objective of our study was to determine the prevalence rates of metabolic syndrome in a group of patients receiving antipsychotic treatment and also in the subgroups treated with different antipsychotic medication. We focused on long-lasting treatment with antipsychotics because the efficacy and safety of these psychopharmacs in acute treatment have been studied many times before.

Methods

The study group consisted of 71 patients, 31 males and 40 females, all of whom have received antipsychotic medication for at least one year. From all the patients hospitalized at the Clinic of Psychiatry in Martin Faculty Hospital in the years 2004 – 2008 we had selectively chosen those who were on antipsychotic monotherapy for at least 12 months. The only accepted concomitant medications were anxiolytics and hypnotics. Many patients receiving antipsychotic did not meet inclusion criteria because of short treatment duration or because they were treated with combination of psychopharmacs. That is why the number of included patients was not higher. The average age of the participants was 37.1 ± 10.4 years. 12 % of the patients suffered from affective disorders – either accompanied with psychotic symptoms or manic episode or remission and recovery of bipolar disorder. 35 % suffered from schizophrenia, 36 % suffered from schizoaffective disorder and the rest of the group (17 % of the patients) suffered from other schizophrenia spectrum disorders. 22 patients were treated with olanzapine, 20 patients were treated with quetiapine, 16 patients received amusulpirid, 8 received sertindol and 5 patients received risperidon. In each patient, blood samples were taken to examine fasting plasma glucose, HDL cholesterol and triglycerides concentrations together with liver enzymes, total and direct bilirubin and plasma immunoreactive insulin (IRI) levels. At the same time we measured anthropometric indices including body weight, height, body mass index (BMI), waist circumference and body fat percentage using Omron HBF-306 Body Fat Analyzer. Also patients´ blood pressure (BP) and heart rate were monitored. According to criteria for diagnosing metabolic syndrome established by International Diabetes Federation (IDF) we assessed its prevalence in the whole study group and observed differences among patients receiving olanzapine, quetiapine, amisulpirid, sertindol a risperidon.

According to the IDF definition, for a person to be defined as having metabolic syndrome, he must have central obesity, defined as waist circumference ≥94 cm for Europid men and = 80 cm for Europid women, plus any two of the following four factors:

a) raised triglycerides: ≥1.7 mmol/L,
b) reduced HDL-cholesterol: <1.03 mmol/L in males and <1.29 mmol/L in females, or specific treatment for these lipid abnormalities,
c) raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension,
d) impaired fasting glycaemia (IFG): fasting plasma glucose ≥5.6 mmol/L, or previously diagnosed type 2 diabetes.

We also assessed its relation to the age and sex as well as correlations between individual metabolic syndrome components and other variables. The obtained data were processed by statistics programme STATISTICA 8.0. For detection of correlations between various parameters Spearman's rank correlation test was used.

Results

The prevalence of metabolic syndrome in our sample of 71 patients on long-term treatment with atypical antipsychotics reached 41 %. The highest metabolic syndrome prevalence rate of 50 % was noted in the olanzapine subgroup. Identical percentage of patients suffering from metabolic syndrome occured in quetiapine and risperidone subgroups reaching 40 %. The lowest prevalence of 25 % and 31 % was observed in sertindol and amisulpirid subgroup, respectively. The prevalence rate of metabolic syndrome in men was 51 % compared to 34 % in women.

In the total of 71 patients the presence of individual components of the metabolic syndrome differed. Central obesity – an essential criterion for diagnosing metabolic syndrome was met in 86 % of females and in 69 % of males, it means in 79 % of all patients. Elevated triglyceride levels were detected in 48 % of the patients while low HDL cholesterol levels were detected in 12 % of the patients. In 36 % of the participants, including those two with previously diagnosed type 2 diabetes, raised fasting plasma glucose was found out. Raised blood pressure was detected in 38 % of the patients. Except central obesity, all other risk factors included in the metabolic syndrome occured more frequenly in men than in women. The prevalence rates of all components together with gender differences are presented in Table 1.

Tab. 1. The prevalence rates of metabolic syndrome and its components.

Cardiovascular risk factor	Prevalence (%)	Men (%)	Women (%)
Metabolic syndrome	41	51	34
Central obesity	79	69	86
Elevated triglycerides	48	60	40
Low HDL cholesterol	12	16	9
Impaired fasting glycaemia	36	43	32
Hypertension	38	51	28

Tab. 2. The prevalence of overweight and obesity according to WHO classification.

BMI (kg/m^2) range	WHO classification	Prevalence in our group
<18.5	Underweight	0%
18.5–24.9	Normal range	32%
25.0–29.9	Preobese	32%
30.0–34.9	Obese class 1	21%
35.0–39.9	Obese class 2	10%
≥40.0	Obese class 3	5%

We also assessed the number of atherogenic features of the metabolic syndrome besides central obesity carried by study members. 23 % of the patients carried 1 atherogenic feature. 32 % were carriers of 2 metabolic syndrome risk factors, identically 32 % of the patients were carriers of 3 metabolic risk factors except central obesity and in 13 % of them all 4 atherogenic features including raised triglycerides, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose were present.

Another aim of the study was to clarify the relationships among individual metabolic syndrome components and between them and other variables. We found a positive correlation between waist circumference and triglycerides ($r = 0.42$, $p < 0.05$) fasting plasma glucose (0.21, $p < 0.05$) and insulin concentration (0.51, $p < 0.05$) as well as systolic blood pressure. It positively correlated with treatment duration (0.29, $p < 0.05$), body weight (0.84, $p < 0.05$), body fat percentage (0.61, $p < 0.05$), body mass index (0.9, $p < 0.05$) and liver enzymes ALT (0.28, $p < 0.05$) and GMT (0.54, $p < 0.05$). There was s negative correlation between waist circumference and HDL cholesterol concentration (–0.45, $p < 0.05$).

Triglyceride levels negativily correlated with HDL cholesterol (–0.29, $p < 0.05$) and bilirubin levels, both total (–0.27. $p < 0.05$) and direct (–0.38, $p < 0.05$) and there was a positive correlation with ALT (0.26, $p < 0.05$), GMT (0.47, $p < 0.05$), insulin (0.36, $p < 0.05$), body weight (0.31, $p < 0.05$), BMI (0.29, $p < 0.05$), and waist circumference as already mentioned.

Comparing HDL levels with other variables, we found negative correlations with AST (–0.21, $p < 0.05$), ALT (– 0.36, $p < 0.05$) and GMT (–0.34, $p < 0.05$) levels, then triglycerides (–0.29, $p < 0.05$), insulin levels (–0.29, $p < 0.05$) and anthropometric parameters including body weight (–0.47, $p < 0.05$), BMI (–0.39, $p < 0.05$), waist circumference (–0.45, $p < 0.05$) and body fat percentage (–0.31, $p < 0.05$).

Another negative correlation was observed between systolic blood pressure and heart rate (–0.22, $p < 0.05$) as well as body fat percentage (–0.23, $p < 0.05$).

Fasting plasma glucose positively correlated with age (0.44, $p < 0.05$), treatment duration (0.45, $p < 0.05$), insulinemia (0.25, $p < 0.05$), liver enzymes GMT (0.21, $p < 0.05$) and ALP (0.27, $p < 0.05$), also waist circumference (0.21, $p < 0.05$) and heart rate (0.36, $p < 0.05$).

Using the international classification of adult underweight, overweight and obesity according to BMI established by the World Health Organization (WHO) we identified that 32% of the patients were of normal weight (36 % women vs 26 % men). The same percentage of patients suffered from overweight (30 % women vs 34 % men) and the rest of the study group (36 %) had BMI score indicating obesity. Class I obesity was present in 21 % of the participants, more frequently in males (23 % men vs 20 % women), class II obesity in 10 %, also more frequently in males (14 % men vs. 8 % women) and class III obesity in 5 % of the participants, more frequently in females (6 % women vs 3 % men). The prevalence of overweight and obesity according to WHO classification is presented in Table 2. BMI values positively correlated with body fat percentage as well as with central obesity. According to Deurenberg´s recommendations for interpretation of measured body fat percentage we found out that 28 % of the patients had normal body fat ratio, high body fat content was measured in 30 % of them and too high body fat content was measured in as many as 42 % of the patients.

Discussion

As we expected, the prevalence of the metabolic syndrome in our sample of patients on long-term treatment with atypical antipsychotics reached high value. Suprisingly, it was the same percentage (41 %) of patients like McEvoy and others (8) observed in their study with schizophrenia patients. Nevertheless, we found differences in its prevalence when comparing males and females. In our study group the prevalence rate of metabolic syndrome was higher in men than in women (51 % vs 34 % in women) in contrast to higher prevalence in women (52 % vs 36 %) reported by these authors. Our results suggest that men are more likely to carry any component of the metabolic syndrome except central obesity. Among metabolic syndrome features central obesity occured most frequently – in 71 % of the patients. This was followed by elevated triglyceride levels (42 %), raised blood pressure (38 %), and fasting plasma glucose (36 %) and rarely occurring reduced HDL cholesterol (12 %).

Objective of our study was also to evaluate whether atypical antipsychotis – olanzapine, quetiapine, amisulpirid, sertindol and risperidon – differ regarding their impact on the cardiovascular disease risk profile. According to metabolic syndrome prevalence rates in the subgroups treated by different antipsychotic, olanzapine appears to be associated with the highest cardiovascular risk as 50 % of the patients receiving this medication suffered from metabolic syndrome. Quetiapine and risperidone treated patients met criteria for metabolic syndrome identically in 40 % and the lowest risk of metabolic syndrome was in amisulpirid (31 %) and sertindol (25 %) subgroup.

Among the components of metabolic syndrome only waist circumference correlated significantly with all other features what confirms the most widely accepted theory describing the complicated interaction between metabolically active visceral adipose tissue and resultant insuline resistance. The presence of visceral obesity is thought to be atherogenic due to increased lipolysis and release of nonesterified free fatty acids (FAAs). The elevated hepatic and plasma FAA concentrations result in abnor-

mal gluconeogenesis or glucose dysregulation. Other by-products of adipose tissue that damage the vascular system include interleukin-6, tumor necrosis factor-α, angiotensinogen, adipsin and leptin (9–11). Beside causing direct endothelial dysfunction, TNF-α decreases the activity of lipoprotein lipase, which causes atherogenic dyslipoproteinemia or elevated triglycerides and decreased HDL. The resistance to insulin also decreases lipoprotein lipase activity and leads to dyslipidemia. Hyperinsulinemia increases the activity of the sympathetic nervous system, which can lead to hypertension. As resistance to insulin progresses, insulin loses its ability to effect vasodilatation, which can further increase blood pressure (12).

Despite high metabolic syndrome prevalence observed in patients treated with second generation antipsychotics, these drugs don´t appear to be the only causation of higher prevalence of metabolic disturbances. Data suggest that schizophrenia patients have higher rates of diabetes, one of the components of metabolic syndrome, independent of medications taken (13). So, the illness itself may contribute to development of the metabolic disturbances.

One set of explanations for greater vulnerability to certain illnesses points also to the lifestyles of individuals with serious mental illnesses. It´s known they usually tend to lead sedentary life and to buy cheap, high-calorie foodstuffs in consequence of lack of financial resources. Consequently, poor dietary habits, obesity, high rates of smoking and partly antipsychotic medications themselves may contribute to increased risk of cardiovascular diseases in treated patients.

Despite the recognition of elevated risks of medical comorbidity in schizophrenia and other mental illnesses, the detection and treatment of these comorbidities remains poor at present. Although metabolic risk profile of individual antipsychotics differs and our results indicate that olanzapine is most likely to induce metabolic side effects, regular monitoring for metabolic disturbances is essential for all patients no matter the antipsychotic they receive. Only right monitoring allows early detection leading to appropriate interventions. These may substantially lower the risk of cardiovascular disease, that dominates as the number one cause of death in patients with schizophrenia.

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