Metabolic Risk Factors in Drug-Naive Patients With First-Episode Psychosis

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Objective: Metabolic risk factors, such as obesity, as well as abnormalities in glucose and lipid metabolism, have been shown to have an increased prevalence in patients with schizophrenia, especially in those treated with antipsychotic medication. However, studies looking at these abnormalities in drug-naive patients have been few in number and have yielded mixed results. The aim of our study was to look at the prevalence of some of the cardiovascular risk factors, such as obesity and lipid and glucose abnormalities, in drug-naive patients with first-episode psychosis compared to healthy controls matched for age, gender, and ethnicity.

Method: One hundred sixty patients aged between 18 and 40 years who presented to the Early Psychosis Intervention Programme in Singapore with a diagnosis of first-episode psychosis according to the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition were assessed for their body mass index (BMI) and plasma levels of fasting glucose and lipids. The results of this assessment were compared to similar data from 200 controls matched for age, gender, and ethnicity, collected as part of an annual workplace health screening. The study was conducted from June 2002 to March 2005.

Results: There were significant differences in the mean baseline weight, BMI, and plasma levels of total and LDL cholesterol; all of these values were significantly higher in the controls compared to patients ($p < .005$ for all). Controls were significantly more likely to have high BMI (≥ 23 kg/m^2) and high LDL cholesterol level (> 3.4 mmol/L) as compared to patients ($p < .005$ and $p = .01$, respectively). However, patients compared to controls were significantly more likely to have diabetes ($p = .007$).

Conclusion: The link between diabetes and psychotic illness previously reported in relatives of patients with schizophrenia and in medication-naive patients implies a possible genetic link between schizophrenia and abnormal glucose metabolism. However, the finding of low prevalence of obesity and dyslipidemia at the onset of illness suggests that the increased frequency of these abnormalities in patients is an effect of their antipsychotic medication.

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Patients with schizophrenia have a mortality rate that is almost 3 times higher than the general population.[1] Although death due to unnatural causes such as suicide is high among patients with schizophrenia, almost two thirds of the excess mortality can be accounted for by deaths caused by natural causes.[2] A Swedish-population study found that, among 7784 patients, the most common causes of natural deaths were cardiovascular disease and cancer,[3] and similar results were reported by Brown et al.[4] in a smaller U.K. study.

Obesity, as well as abnormalities in glucose and lipid metabolism, are known risk factors in cardiovascular disease and have been shown to have an increased prevalence in patients with schizophrenia.[5,6] In the last decade, numerous studies have conclusively shown a link between these metabolic abnormalities and antipsychotic medications, especially clozapine and olanzapine.[7,8]

It is, however, also possible that shared genetic susceptibility for schizophrenia and impaired metabolism, as well as lifestyle issues (smoking, poor nutrition, sedentary lifestyle), may account for the increased risk of cardiovascular disease in patients.[9] In addition, high autonomic activity secondary to prolonged stress and nicotine can produce increased secretion of epinephrine,[10,11] which is known to be diabetogenic, as well as cause increase in cholesterol levels.[12]

Newly diagnosed patients with first-episode psychosis give us the unique opportunity to look at the prevalence of metabolic abnormalities in patients who have not been exposed to antipsychotic treatment and are relatively younger than the patients with chronic schizophrenia. However, studies looking at these abnormalities in drug-naive patients have been very few and have shown mixed results. Spelman et al.[13] reported that drug-naive schizophrenia patients had

significantly higher frequency of impaired glucose tolerance compared to controls. However, they found that the levels of fasting glucose, total cholesterol, and high-density lipoprotein (HDL) cholesterol were comparable between patients and healthy controls. Zhang et al.[14] found no differences in plasma levels of fasting glucose, insulin, and lipid profile between 46 drug-naive patients and 38 controls. A recent study looking at 38 minimally treated patients with first-episode psychosis compared to 36 healthy controls found that patients did not differ from healthy controls in levels of fasting glucose, insulin, and glycated hemoglobin and in lipid abnormalities.[15] However, all these studies had a small sample size, and, except for one,[14] had been conducted on a Western population.

The aim of our study was to look at the prevalence of some cardiovascular risk factors, such as obesity and lipid and glucose abnormalities, in drug-naive patients with first-episode psychosis compared to healthy controls matched for age, gender, and ethnicity. Our hypothesis was that patients would have a higher prevalence of risk factors than controls.

METHOD

Singapore is an island-state in Southeast Asia with a population of 3.4 million, the majority of which is Chinese (77.7%) followed by Malays (14.2%), Indians (7.2%), and others (1.2%). One hundred sixty patients who presented with first-episode psychosis to the Early Psychosis Intervention Programme (EPIP) in Singapore were included in the study. The EPIP, which is a nationwide program, was launched in 2001 at the Institute of Mental Health/Woodbridge Hospital, the only state psychiatric hospital in Singapore.

The patients fulfilled the following criteria: (1) they were aged between 18 and 40 years; (2) they had first-episode psychotic disorder with no prior or minimal treatment, i.e., less than 72 hours of antipsychotic medications; and (3) the psychosis was not secondary to substance abuse or medical problems. Informed consent was taken from the patients who expressed their willingness to participate in the study, and institutional review board approval was obtained. Their diagnosis was assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition,[16] and their sociodemographic data were obtained using a semistructured questionnaire. In addition, weight (kg) and height (m) were measured and body mass index (BMI) was calculated. Blood samples were taken from all subjects in the morning after a 12-hour overnight fast. Blood was withdrawn into Vacutainer tubes for measurement of blood glucose and for lipid analysis. Total cholesterol, HDL, low-density lipoprotein (LDL) cholesterol, and glucose levels were determined enzymatically by using SYNCHRON LX System(s), UniCel DxC 600/800 System(s), and SYNCHRON Systems Lipid Calibrator.

For the control group, we used anonymised data that were collected as part of an annual workplace health screening. Two hundred control subjects were matched for age, gender, and ethnicity to the patient population, and their data were used in the final analysis. We further classified those with BMI < 23.0 as having normal BMI and those with BMI ≥ 23.0 as having high BMI based on the BMI cutoff levels for Singapore, which were revised based on the findings from local studies and the recommendations from the World Health Organization (WHO) Expert Consultation in Singapore.[17] Low-density lipoprotein cholesterol levels < 3.4 mmol/L were classified as normal, and values above this cutoff were classified as high. Diabetes was defined according to the WHO criteria as a fasting blood glucose levels > 6.1 mmol/L.[18] We then compared these categories between patients and controls. The study was conducted from June 2002 to March 2005.

Statistical Analyses

All statistical analyses were carried out using SPSS 16.0 software (SPSS Inc., Chicago, Ill.). Differences between patients and controls were assessed using Pearson χ^2 tests for categorical data, t tests for parametric nominal data, and Mann-Whitney U tests for nonparametric nominal data. All p values were 2-tailed, and statistical significance was set at $p < .05$.

RESULTS

The mean (SD) age of the patients was 30.0 (6.5) years. Of the patients, 54.4% were male. The majority of the patients were Chinese (N = 119 [74.4%]), followed by Malays (N = 25 [15.6%]), Indians (N = 13 [8.1%]), and those belonging to other ethnicities (N = 3 [1.9%]). The diagnoses of patients included in the study were schizophrenia spectrum disorder (N = 113 [70.6%]), affective psychoses (N = 9 [5.6%]), psychosis not otherwise specified (N = 19 [11.9%]), and other psychotic disorders (N = 19 [11.9%]). The mean (SD) duration of untreated psychosis in patients since change in symptoms was 18.3 (36.7) months and ranged from a minimum of 0.1 months to 264.0 months.

There were no significant differences between the patients and controls with regard to age, ethnicity, and gender distribution since they were originally matched for these. There were significant differences in the baseline weight, BMI, and plasma levels of total and LDL cholesterol; all of these measures were significantly higher in the controls compared to patients ($p < .005$ for all). Controls were significantly more likely to have high BMI (≥ 23 kg/m^2) and high LDL cholesterol level (> 3.4 mmol/L) as compared to patients ($p < .005$ and $p = .01$, respectively). However, patients were significantly more likely to have diabetes compared to controls ($p = .007$). There were no significant differences between the 2 groups with regard to the levels of HDL cholesterol (Table 1).

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Table 1. Baseline Sociodemographic Characteristics and Metabolic Indices of Patients and Controls

Variable	Patient (N = 160)	Control (N = 200)
Age, mean ± SD, y	30 ± 6.5	30.2 ± 5.5
Gender, N (%)		
Male	87 (54.5)	100 (50.0)
Female	73 (45.6)	100 (50.0)
Weight, mean ± SD, kg**	57.6 ± 12.3	62.1 ± 14.6
BMI, mean ± SD, kg/m²**	21.2 ± 3.7	23.5 ± 4.4
BMI ≥ 23.0, N (%)**	43 (26.9)	104 (52.0)
Total cholesterol, mean ± SD, mmol/L**	4.7 ± 1.0	5.1 ± 0.9
LDL cholesterol, mean ± SD, mmol/L**	2.7 ± 0.9	3.1 ± 0.8
LDL > 3.4 mmol/L, N (%)*	36 (21.3)	69 (32.5)
HDL cholesterol, mean ± SD, mmol/L	1.5 ± 0.4	1.5 ± 0.3
Diabetes, N (%)*	8 (5.0)	1(0.5)

*p < .05.
**p < .005.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

DISCUSSION

We had hypothesized that, due to unhealthy lifestyle habits or a genetic predisposition, the patients with first-episode psychosis would have more metabolic risk factors even before they were started on antipsychotic medication. The results from our study were mixed. A significantly higher proportion of patients had abnormal fasting blood glucose levels compared to controls, and a significantly higher proportion of controls had an abnormal BMI and LDL and total cholesterol levels compared to patients. Obesity is a well-recognized risk factor for development of diabetes; hence, the finding that patients had a higher prevalence of diabetes, even though they had a significantly lower BMI, was surprising. However, similar findings were reported by Ryan and colleagues[19] in their study in which 26 drug-naive schizophrenic patients were compared to 26 controls matched in terms of age, BMI, smoking and physical exercise habits. Their results showed that patients had significantly higher fasting glucose and insulin levels, even though they had significantly lower total and LDL cholesterol levels. The researchers did find a positive correlation between indirect measures of visceral obesity, such as waist-to-hip ratio, waist circumference, and plasma levels of glucose. Unfortunately, in our study, we did not include these measures. But Ryan and colleagues[19] do raise doubts as to whether obesity is an independent risk factor for developing diabetes, especially in patients with schizophrenia, a disorder in which the dysfunction of hypothalamus-pituitary-adrenal axis, which causes hypercortisolemia, may account for excessive amounts of visceral fat deposition and development of impaired glucose metabolism. The link between diabetes and psychotic illness has been reported in the pre-antipsychotic era,[20] and a high prevalence of diabetes has been found in relatives of patients with schizophrenia,[21] a finding that also implies possible genetic link between schizophrenia and abnormal glucose metabolism.

Interestingly, in terms of their BMI and lipid metabolism, the patients in our study were significantly healthier than the controls. In 3 population-based cohort studies,[22–24] researchers found that mean BMI and weight of pre-schizophrenic young men were significantly lower as compared to their peers; in fact, there was an inverse relationship between young adult BMI and risk of developing schizophrenia. One of the articles[24] speculates that early environmental factors (i.e., low birth weight, poor nutrition) or perhaps the presence of prodromal symptoms, such as depression with diminished appetite, may explain the observed association between low BMI and risk of developing schizophrenia. All 3 studies were conducted only in males and, hence, it is difficult to generalize the findings to the rest of the population. But the findings from the studies looking at pre-schizophrenic cohorts and our study looking at first-episode psychosis patients allude to the possibility that patients have in fact lower BMI and perhaps lipid abnormalities before and even at the onset of the illness and that a dramatic emergence of these risk factors occurs after the initiation of treatment. A recent study[25] found that, at baseline, the percentages of patients with first-episode psychosis and healthy controls who were overweight, dyslipidemic, hyperglycemic, and hyperinsulinemic did not differ; however, 6-month treatment with antipsychotics was associated with exacerbation of preexisting and emergence of new cardiovascular risk factors.

Our study had a few limitations: data on our control subjects were obtained from a workplace health-screening survey, and we did not do face-to-face assessment of these subjects to screen out for presence of psychiatric diagnoses; but, in general, this cohort of subjects was representative of the general population. Unfortunately, we did not obtain information on the dietary (including alcohol use) patterns, smoking status, and exercise practices of either group of subjects, and these factors could have had a significant effect on the BMI and metabolism. We also did not measure waist circumference or waist-hip ratio to determine the effects of adiposity on blood glucose levels.

Nevertheless, this is, to our knowledge, the first large-scale study looking at the metabolic indices in drug-naive patients with first-episode psychosis in an Asian setting. The findings from our study once again reinforce the need for careful selection of the right antipsychotic drug for each patient and regular monitoring of BMI, blood pressure, and serum glucose and lipid levels in addition to encouraging him or her to quit smoking, eat healthy meals, and exercise regularly.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa).

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