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The comparison of glycometabolism parameters and lipid profiles between drug-naïve, first-episode schizophrenia patients and healthy controls

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ABSTRACT

To compare the difference in body mass index (BMI), waist-to-hip ratio (WHR), and glucose and lipid metabolism parameters between drug-naïve, first-episode schizophrenia patients and healthy controls matched for age, ethnicity and gender, we conducted a test including BMI, WHR, and fasting glucose and lipid metabolism parameters in both 70 drug-naïve, first-episode schizophrenia patients, having not a single day of cumulative exposure to antipsychotic medications and 44 normal healthy controls at baseline. Student's t tests (two tailed) were conducted to examine between group differences. We found that drug-naïve first-episode schizophrenia patients had higher insulin, insulin resistance and C-peptide levels, and had lower total cholesterol (TC), high density lipoprotein cholesterol (HDL-c) and apolipoproteinA1 levels. Simultaneously, drug-naïve, first-episode schizophrenia patients show a potential tendency of WHR enlargement, although there were no statistically significant differences between groups (mean = 0.82, SD = 0.06, for the patients versus mean = 0.79, SD = 0.06, for the health subjects). These results suggest that drug-naïve, first-episode schizophrenia patients do differ from healthy controls in their fasting glycometabolism parameters and lipid profiles, including fasting plasma levels of insulin, C-peptide, TC, HDL-c, and apolipoproteinA1, and patients are more insulin resistant before the onset of antipsychotic medication treatment.

1. Introduction

The incidence of metabolic syndrome (MS) in schizophrenia population is twice as that in the general population, and there exists higher prevalence of glucose and lipid metabolism abnormalities in schizophrenia patients (Boehm et al., 2004; Casey et al., 2004; Leslie and Rosenheck, 2004; Wu et al., 2006; Yogaratnam et al., 2013). But so far, the mechanism is still unclear. A great amount of evidence has suggested that antipsychotic medications may play an important role therein. For example, the induction of glucose elevation by antipsychotics has been reported since the introduction of chlorpromazine in the mid-1950s. Other so-called "low potency" agents such as thioridazine and mesoridazine were also reported to induce glucose increase (Bernstein, 1987). Later, atypical antipsychotic medications were added to this list (Kamran et al., 1994; Poyurovsky et al., 2002; Howes et al., 2004; Citrome, 2005; Palik et al., 2005), and significant elevations in triglyceride and cholesterol levels were also reported in association with atypical antipsychotic treatment (Meyer, 2002). However, substantial study proofs have also shown that patients with schizophrenia have an increased risk in developing diabetes mellitus regardless of antipsychotic medications (Dixon et al., 2000). Using the frequently sampled intravenous glucose tolerance test and minimal model analysis, Cohn reported that young drug-free patients with schizophrenia had insulin resistance and were susceptible to type II diabetes mellitus independent of antipsychotic medication usage (Cohen et al., 2006). The rate of type II diabetes mellitus in family members of schizophrenia patients is 18% to 30% (Mukherjee et al., 1989), which is far higher than that in the general population at large (1.2%–6.3%) (Adams and Marano, 1995). It was also reported in a recent study that the siblings of schizophrenia probands had a significantly increased two-hour mean glucose concentration compared to the control subjects (Fernandez-Egea et al., 2008). Therefore, patients with schizophrenia and their first-degree relatives appear to be predisposed to developing type II diabetes mellitus. What is more, studies conducted in the preneuroleptic era also support the hypothesis that type II diabetes mellitus may occur more commonly

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in schizophrenia than expected (Ryan and Thakore, 2002). To disentangle the effects of antipsychotic medications from baseline abnormalities, some recently published studies (Ryan et al., 2003; Spelman et al., 2007) showed that up to 10%–16% of patients with first-episode, drug-naïve schizophrenia had impaired fasting glucose tolerance, and patients were more insulin resistant and had higher levels of plasma glucose, insulin and cortisol, compared to healthy controls. However, controversy still exists. A similar study (Sengupta et al., 2008) conducted with drug-naïve, first-episode psychosis patients with a diagnosis of schizophrenia spectrum disorder reported that no significant differences of glycometabolism parameters and lipid profiles between patients and healthy subjects were found.

It has been debated whether schizophrenia itself or antipsychotic medications are primarily responsible for the observed increased metabolism disturbances, but the present investigation provides the evidence that schizophrenia itself may be linked with the prevalence of glucose and lipid metabolism abnormalities independently of antipsychotic medication administration.

In this study, we compared baseline glycometabolism parameters and lipid profiles between drug-naïve, first-episode schizophrenia patients and age, sex, and ethnicity matched healthy controls in a Chinese Han nationality.

2. Materials and methods

2.1. Study design

This was a prospective, open-label, observational study conducted under naturalistic situations from October 2009 to March 2012. At baseline, the fasting glucose, fasting insulin, C-peptide, cholesterol, triglyceride, apolipoproteinA1 and apolipoproteinB100 levels of all subjects were assessed by members of a trained independent research team. To ensure that the patients underwent fasting, we assigned two nurses to take special care of the subjects. The symptom severity of all patients was rated by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on admission.

2.2. Study participants

All subjects are Chinese descendants. Seventy drug-naïve, first-episode schizophrenia patients are inpatients from the psychiatric department, the Third Affiliated Hospital of Sun Yat-sen University. DSM-IV diagnosis of schizophrenia was established using SCID performed by a single experienced psychiatrist (ZHZY) and reviewed by a senior psychiatrist (ZHJB). All patients were experiencing their first-episode schizophrenia and were drug-naïve, and met the study exclusion criteria, including past major mental illness (psychotic, mood, or anxiety disorder), co-morbid DSM-IV diagnosis of alcohol or illicit drug abuse, and eating disorder. All patients received a thorough medical checkup to be physically healthy. To confirm the schizophrenia diagnosis, all patients were followed up for at least 6 months after discharge. All patients were ensured that they had not used any antipsychotics or other recreational drugs before enrollment.

44 healthy volunteers were recruited through advertising from Sun Yat-sen University students, the same hospital employees, and from local enterprise employees. Mental health history was evaluated using the SCID non-patient edition (SCID-NP), and only those without past or concurrent major mental disorder (psychotic, mood, or anxiety disorder) were included in the study. Based on clinical interview, all control subjects were physically healthy and met the following exclusion criteria of having a history of hypertension, cardiac dysfunction, abnormal thyroid function and co-morbid DSM-IV diagnosis of alcohol or illicit drug abuse, and eating disorder.

Common exclusion criteria for both patients and controls included the presence of having a personal or family history of type II diabetes mellitus and refusal to provide written informed consent and refusal to receive PANSS assessments before participating in the study.

After a complete description of the study to the subjects, written-informed consent was obtained in accordance with the National Health and Medical Research Council guidelines. The study protocol was previously reviewed and approved by the ethics committee at the Third Affiliated Hospital of Sun Yat-sen University.

2.3. Assessments

Assessments for the present analysis included fasting blood samples for glucose, insulin, C-peptide, cholesterol, triglyceride, apolipoproteinA1 and apolipoproteinB100 levels at baseline. Only results of blood samples collected at morning fasting times were included in the analysis. Blood samples of all subjects were collected between 9:00 a.m. and 10:00 a.m. after a 12-h overnight fast. Blood was drawn from an antecubital vein into an EDTA-containing tube for measurements of fasting plasma levels of glucose, insulin, C-peptide, and lipid profiles.

Plasma glucose measurement (mmol/l) was determined by the enzymatic photometric test (GOD-PAP) method (DiaSys Diagnostic System GmbH, Germany). Plasma insulin levels (mU/l) were tested from ADVIA Centaur by using direct chemiluminescence method (Siemens Healthcare Diagnosis Inc. Massachusetts, USA). The sensitivity of the assay was 0.5 mU/l. Intra- and inter-assay coefficients of variation were 3.3%–4.6% and 4.8%–5.9%, respectively. The same method was applied to detect the plasma C-peptide levels (ng/ml), and the sensitivity of the assay was 0.05 ng/ml. Intra- and inter-assay coefficients of variation were 3.7%–4.1% and 1.0%–3.3%, respectively. The formula for the homeostasis assessment model is as follows: insulin resistance index (IRI) = fasting insulin (10^3 μU/l) × fasting glucose (mmol/l) / 22.5 (Haffner et al., 1997).

Plasma apolipoproteinA1 and apolipoproteinB100 levels were measured by the immunoturbidimetry method (Sichuan Maker Biotechnology Co., Ltd. Chengdu, China). The range of detectable level for plasma apolipoproteinA1 was 0–2.00 g/l and for apolipoproteinB100 was 0–2.50 g/l. Inter-assay coefficients of variation were ≤5% for both apolipoproteinA1 and apolipoproteinB100.

Fasting plasma levels of total cholesterol (TC), triglyceride and high-density lipoprotein cholesterol (HDL-c) were analyzed enzymatically by using commercial (Sichuan Maker Biotechnology Co., Ltd. Chengdu, China). The fasting plasma levels of low-density lipoprotein cholesterol (LDL-c) were calculated by using the formula of Friedewald et al. (1972).

For all subjects, anthropometric measurements (weight, height, and waist and hip circumference) were made after participants had removed their shoes and upper garments, and had donned an examining gown. The measurement of waist circumference was taken at the point midway between the iliac crests and the costal margins and hip circumference was measured at the level of the widest circumference. The waist-to-hip ratio (WHR) was used as a measure of upper body adiposity. Body mass index (BMI) was computed as body weight (in kilogram) divided by the square of height (meters^2).

2.4. Statistical analysis

SPSS for Windows (version 13.0, Chicago, Illinois, USA) was used to compare the clinical and demographic characteristic variables between patients and healthy subjects. Demographic characteristics were compared using χ^2 or independent t-tests as appropriate (two tailed). The comparison of clinical observed variables between groups was performed by Student's t tests (two tailed). Spearman correlation analysis was used to assess the possible association between fasting plasma levels of HDL-c and the severity of symptoms. Pearson's product-moment correlation analysis was used to analyze the association between fasting plasma levels of HDL-c and apolipoproteinA1. All statistical tests were evaluated at the 5% significance level.

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