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Male sex may be associated with higher metabolic risk in first-episode schizophrenia patients: A preliminary study

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ABSTRACT

Background: High incidence of metabolic syndrome has been evidenced in schizophrenia patients. However, gender-specific relationship with risk of metabolic disorders in first-episode schizophrenia has received poor systematic study.
Aim: We aimed at exploring the impact of sex difference on the parameters of glucolipid metabolism in first-episode psychosis schizophrenia (FEP) patients.
Methods: We performed a post hoc analysis of data from our previously performed clinical trial. A total of 60 FEP patients and 28 healthy sex- and age-matched volunteers were included. Blood glucose and lipid metabolic profiles, as well as schizophrenia-related clinical symptoms were assessed. The body mass index, level of blood insulin and the homeostasis model assessment-insulin resistance index (HOMA-IR) were measured.
Results: The FEP patients demonstrated significant increases in blood insulin concentration, insulin resistance and blood triglyceride when compared with healthy controls. In FEP patients, there were no differences in psychopathology measurements between the genders. BMI and HOMA-IR were significantly greater in male vs female FEP patients. In addition, a more severe dyslipidemia was also observed in male FEP patients, including an increased triglyceride level, an augmented LDL content and a decreased HDL concentration. Multivariate linear regression analysis demonstrated that the gender was significantly correlated to HOMA-IR.
Conclusion: These preliminary results suggest that male FEP patients may be more predisposed to insulin resistance and dyslipidemia than female FEP patients. These results could contribute to the understanding of prevention and treatment of metabolic syndrome in FEP patients.
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1. Introduction

A multitude of studies have evidenced **s**chizophrenia is related to components of the metabolic syndrome (MetS), which is identified by cluster of visceral obesity, impaired lipid metabolism, hyperglycemia and hypertension. A lot of studies have showed higher cardiovascular mortality and shortened life span in these patients (Brown, 1997; Capasso et al., 2008; Curkendall et al., 2004; Lakka et al., 2002; Ryan and Thakore, 2002; Saha et al., 2007). Mechanism underlying the high incidence of metabolic disorders among schizophrenia people is not well illuminated. Explanations like poor lifestyle, dietary habits and direct effect of psychotropics on metabolic disturbances have been established.

Moreover, schizophrenia itself has been found to be an important risk factor for MetS (Lindenmayer et al., 2001; Mohan et al., 1999; Ryan et al., 2003). Potential mechanisms for comorbidity of schizophrenia and MetS including inflammation (Bauer et al., 2007; Deng et al., 2013; Fillman et al., 2013; Monje et al., 2003; Watanabe et al., 2010), growth factors such as brain-derived neurotrophic factor (BDNF) (Ernst et al., 2012; Unger et al., 2007), perturbations in common neuroendocrine regulatory pathways such as hypothalamic–pituitary–adrenal (HPA) axis (Ryan et al., 2003) and neuropeptide Y (Kuromitsu et al., 2001;

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Morrison and Berthoud, 2007; Raghanti et al., 2013), and shared genetic risk (Alkelai et al., 2012; Hansen et al., 2011) have been proposed. However, previous studies have yielded conflicting results for the relationship between gender and MetS in patients with schizophrenia. Some research has suggested that women are more likely to suffer from MetS (Bener et al., 2014; Huang et al., 2009; Meyer et al., 2005), only a few assert the contrary (Kraemer et al., 2011), while several other studies have showed that there is no gender difference in the incidence of MetS (Bobes et al., 2007; Hagg et al., 2006). Furthermore, gender-specific relationship with metabolic disorders in first-episode schizophrenia has received poor systematic study. In population without schizophrenia, an increased rates of glucolipid metabolic disorders have been evidenced in men as compared in women (Barrett-Connor et al., 2004; Barros and Gustafsson, 2011; Shi and Clegg, 2009). Enhanced visceral fat storage, decreased adiponectin levels and sex hormones may contribute to insulin resistance and higher vulnerability to cardiovascular disorders in males (Mittendorfer, 2005; Nishizawa et al., 2002; Wajchenberg, 2000). Therefore, we performed a post hoc analysis of our previously performed clinical study (http://www.clinicaltrials.gov, trial registration number: NCT01057849), and aimed at exploring the impact of gender difference on the glucose and lipid metabolic profiles in first-episode psychosis schizophrenia (FEP) patients.

2. Methods

2.1. Subjects

We performed a post hoc analysis of data from our previously performed clinical study (http://www.clinicaltrials.gov, trial registration number: NCT01057849). This was a prospective, randomized and open-label study of sequenced atypical antipsychotics therapy with intensive or basic psychosocial intervention for first-episode schizophrenia. The current post hoc analyses are based on the baseline data from Beijing Huilongguan Hospital. Of these, $n = 60$ symptomatic FEP patients were from inpatient department and had relatively complete glucolipid metabolism data. Twenty-eight sex- and age-matched healthy volunteers were included. Clinical diagnosis was confirmed using the patient research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) by two senior psychiatrists. The inclusion and exclusion criteria in the present study have been described in detail elsewhere (Chen et al., 2013). In brief, the FEP patients needed to meet the following criteria: (a) aged 16–45 years (inclusive); (b) duration of symptoms not longer than 3 years; (c) no history of previous treatment with psychotropic drugs or, if previously treated, a total life time usage of less than 14 days; (d) physically healthy and no other metabolic disorders. The study protocol was approved by the local ethics committee (agreement No. 2008-21). Written informed consent was obtained from the study participants and guardians of patients also had provided written informed consent.

2.2. Psychopathology and metabolic parameters measurement

For all subjects, body mass index (BMI, kg/m^2) was calculated by body weight (kg)/[height (m) × height (m)]. Besides, all participants were asked about current tobacco use and divided into smokers and non-smokers. Clinical psychopathology was evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989), and the interviewers were two senior psychiatrists specially trained for this evaluation.

Venous blood from all subjects was collected between 7:00 and 8:00 AM after fasting overnight. Serum was obtained by centrifugation at 3500 rpm for 10 min. Fasting serum glucose, insulin levels and lipid profiles, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were determined by the clinical laboratory of Beijing Huilongguan Hospital, as previously described (Chen et al., 2013). Then, insulin resistance was analyzed by homeostasis model of assessment-insulin resistance index (HOMA-IR) using the following formula: [fasting serum insulin (μIU/mL) × fasting serum glucose (mmol/L)/22.5]; HOMA β-cell function (HOMA-β) according to the formula: [20 × fasting serum insulin (μIU/mL)/(fasting serum glucose (mmol/L) − 3.5)].

3. Statistical analysis

Analysis was carried out using the SPSS 16. HOMA-IR was logarithmically transformed in order to normalize distribution. The independent sample *t*-test was carried out to compare normally distributed continuous variables between two groups, Mann–Whitney's *U*-test was employed for non-normally distributed continuous variables, and Chi-Square test for categorical variables. Associations between variables were assessed using Pearson correlation coefficients. A stepwise multiple linear regression analysis with HOMA-IR as a dependent variable was performed. Data were presented as mean ± standard deviation for continuous variables and the categorical variables were expressed as frequency. All statistical tests were two-tailed and a *P*-value <0.05 was considered to be statistically significant.

4. Results

4.1. FEP patients had higher levels of glycolipid metabolism related parameters

FEP patients showed a significant increase in blood insulin level, as well as an altered insulin resistance (HOMA-IR) and a reinforced pancreatic β-cell function (HOMA-β), when compared to healthy controls (Table 1). Moreover, the blood triglyceride content was higher in first-episode schizophrenia patients. There were no differences for levels of blood glucose and total cholesterol between control and FEP patients.

4.2. In FEP schizophrenia patients, male sex was associated with a more severe alteration of insulin resistance and lipid metabolism

In male and female FEP patients, positive/negative subscale scores, general psychopathology subscale scores, PANSS total scores and disease course were not different. However, smoking rate, BMI and blood insulin level of male patients were larger than those of female patients. Similarly, HOMA-IR was significantly elevated in male patients (Table 2 and Fig. 1A).

Moreover, the male gender showed more important blood level of triglyceride and LDL, whereas the blood HDL level was blunted, when compared to female subjects (Table 2).

4.3. In FEP schizophrenia patients, male sex was an independent risk factor of insulin resistance

Correlation analysis demonstrated that BMI ($r = 0.417$, $P = 0.001$), triglyceride level ($r = 0.269$, $P = 0.038$) and LDL concentration ($r = 0.337$, $P = 0.009$) were positively related to HOMA-IR. Similarly, blood HDL content ($r = -0.257$, $P = 0.047$) was negatively related to HOMA-IR (Fig. 1B–E).

Stepwise multivariate linear regression analysis using HOMA-IR as dependent variable, and BMI, triglyceride, LDL, HDL, gender, smoking habit as independent variables revealed that male sex and increasing BMI were the independent predictive factors of insulin resistance (Table 3). The regression

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