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Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia

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ABSTRACT

Controversial results concerning insulin resistance and lipid metabolism have been reported in antipsychotic-naive first-episode psychosis (AN-FEP) patients with schizophrenia of different countries. We aimed at determining whether schizophrenia-related psychopathology was associated with insulin resistance and/or dyslipidaemia in Chinese patients with AN-FEP schizophrenia. A cross-sectional study was performed in Chinese patients newly diagnosed with schizophrenia ($n = 49$, antipsychotic-naïve or antipsychotic medications $<$ 2 weeks) and healthy volunteers ($n = 30$). The serum levels of insulin and triglyceride levels as well as homeostasis model of assessment-insulin resistance (HOMA-IR) index were significantly increased in AN-FEP patients, when compared with healthy volunteers. The gender difference had a significant impact on the insulin resistance and dyslipidaemia in these AN-FEP subjects. Multiple linear regression analysis demonstrated that the severity of positive symptoms of schizophrenia was negatively related to insulin resistance. No difference of serum glucose level, total cholesterol content, body mass index (BMI) and smoking status was detected between patients with schizophrenia and healthy controls. In conclusion, Chinese AN-FEP patients were more prone to insulin resistance and dyslipidaemia as compared to the healthy population, which is negatively correlated to positive symptoms. The results may contribute to the understanding of the relationship between the glucose/lipidaemia metabolic dysfunction and the psychopathology in patients with schizophrenia.

1. Introduction

Schizophrenia is a life-shortening illness. For all causes of death combined, the mortality risk was doubled in a study by van Os and Kapur (2009). Evidence of increased risk of cardiovascular illness in patients with schizophrenia is more clear-cut. Indeed, circulatory disease was responsible for 20% of deaths in patients with schizophrenia (Newcomer et al., 2009). It was also found that in a 4-year period, observed deaths were twice as numerous as expected and that ischaemic heart disease was the most common cause of death in both sexes of patients with schizophrenia (Herrman et al., 1983).

Metabolic syndrome is a collection of risk factors that are associated with increased morbidity and mortality due to cardiovascular disease (Lakka et al., 2002). Indeed, schizophrenia has long been associated with elements of the metabolic syndrome, and numerous studies have found increased mortality because of cardiovascular diseases (Brown, 1997; Lakka et al., 2002; Ryan and Thakore, 2002; Curkendall et al., 2004). Previous studies reported that poor lifestyle, body weight gain and family history of diabetes mellitus contribute to the onset of diabetes in patients with schizophrenia. Antipsychotic medications have also been considered as an important risk factor for metabolic syndrome (Mohan et al., 1999; Lindenmayer et al., 2001).

Recently, increasing evidences suggest that the schizophrenia itself is implicated in the pathophysiology of diabetes in patients. In the UK, antipsychotic-naive, first-episode psychosis (AN-FEP) patients with schizophrenia had impaired fasting glucose tolerance and were more insulin resistant than healthy comparison subjects (Ryan et al., 2003). In Singapore, AN-FEP patients were significantly more likely to have diabetes when compared to controls (Verma et al., 2009). In Spain, antipsychotic-free FEP patients showed a significantly higher degree of insulin resistance, as measured with

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the homeostasis model of assessment-insulin resistance (HOMA-IR) index, in comparison with the control group (Arranz et al., 2004). However, it has also been reported that in Canada, AN-FEP patients having a schizophrenia spectrum disorder did not differ from healthy controls, in their baseline measures of glucose and lipid metabolites, nor in the prevalence of diabetes or its precursors (Sengupta et al., 2008). This could possibly be due to different populations collected in different clinical studies. It should be noted that previous studies focusing on the increased prevalence of glucose metabolic abnormalities in patients with schizophrenia did not elucidate the relationship between psychopathology and abnormal glucose metabolism.

Therefore, we aimed at determining (1) the prevalence of insulin resistance and lipid metabolism abnormality in Chinese patients with schizophrenia with AN-FEP when compared to healthy controls and (2) whether there is a correlation between the psychopathological symptoms and the metabolic disorders in AN-FEP patients with schizophrenia.

2. Materials and Methods

2.1. Subjects

A total of 49 AN-FEP patients with schizophrenia and 30 matched healthy volunteers were included in this present study. These patients met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria for schizophrenia by agreement of two senior psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association, 1994). The patients with AN-FEP were recruited from inpatients of Hui-Long-Guan Hospital, a city-run psychiatric hospital in Beijing, China. Additional criteria for inclusion in the study were: (1) age between 16 and 45 years; (2) duration of illness <3 years; (3) patients who had never been exposed to or received <2 weeks of antipsychotic medications; (4) patients who were physically healthy; (5) no history of head trauma with loss of consciousness more than 1 h; (6) no lifetime history of substance dependence or abuse within 3 months prior to study participation; (7) no pregnancy or lactation; and (8) no other metabolic diseases. In 49 AN-FEP patients with schizophrenia, 28 patients were drug-free and 21 patients received antipsychotic medications (risperidone, $n=7$; olanzapine, $n=5$; aripiprazole, $n=3$; perphenazine, $n=2$; quetiapine, $n=2$; sulpiride, $n=1$; haloperidol, $n=1$). The study was approved by the local ethics committee. All subjects gave a written informed consent to participate. Participants under 18 years old gave a supplemental written parental consent.

2.2. Analytical methods

For all subjects, body weight (kg) and height (m) were measured and body mass index (BMI, kg m^{-2}) was calculated. Peripheral blood samples from all participants were freshly collected between 7 and 8 AM in a sterile tube containing heparin/ethylene diamine tetraacetic acid (EDTA), following an overnight fast. Blood glucose level and lipid profiles (cholesterol and triglyceride) were determined by Olympus AU2700 automatic biochemical analyser (Beckman Coulter Inc., USA). The serum was then separated by a centrifugation (3500 rpm at 4 °C for 10 min). The insulin level was quantified by commercially available kits based on enzyme-amplified immune-chemiluminescence (Beckman Coulter Inc., USA). Then, insulin resistance was calculated through HOMA-IR, according to the formula, (Fasting serum insulin (μ IU ml^{-1}) $\times$ Fasting serum glucose (mmol l^{-1})/22.5). In addition, smoking status (smoker or non-smoker) was also investigated.

The psychopathology for the patients with schizophrenia was determined by the Positive and Negative Syndrome Scale (PANSS), conducted independently by two psychiatrists on the day of blood sample collection (Kay et al., 1989). To ensure consistency and reliability of ratings across study, both senior psychiatrists underwent training in the use and rating of PANSS together prior to the start of the study. After training, the correlation coefficient >0.8 was maintained for the PANSS total score.

2.3. Statistical analysis

Data analysis was performed by using SPSS 13.0 software. HOMA-IR was logarithmically transformed, when the data were not normally distributed. AN-FEP patients and matched controls were compared by using a Student's *t*-test for parametric nominal data, the Mann–Whitney *U* test for non-parametric nominal data and the Pearson X^2 test for categorical data. Relationships between variables were assessed with Pearson's product moment correlation coefficients, and with partial correlation when controlling for the effects of other additional variables. Stepwise multiple linear regression analysis was used to determine the independent predictors of insulin resistance with a probability value to enter of $P<0.05$ and remove of $P>0.1$. Data were expressed as mean $\pm$ standard deviation (S.D.). $P<0.05$ was considered significant.

3. Results

3.1. Characteristics and metabolic profile of participants

No significant differences of age, gender, BMI and smoking rate were detected between the AN-FEP patients and healthy controls in Chinese population (Table 1). AN-FEP schizophrenia did not affect the fasting serum glucose level (5.1 ± 0.4 and 5.0 ± 0.6 mmol l^{-1} for healthy controls and AN-FEP patients, respectively, $P=0.351$). However, the serum insulin content was significantly increased in AN-FEP patients when compared to healthy volunteers (4.1 ± 1.9 and 6.7 ± 3.8 μIU l^{-1} for healthy control and AN-FEP patients, respectively, $P<0.001$). Similarly, HOMA-IR of AN-FEP patients was more pronounced than that of healthy controls (-0.2 ± 0.4 and 0.2 ± 0.6 for healthy controls and AN-FEP patients, respectively, $P=0.001$, Fig. 1). Concerning lipid metabolism-associated parameters, the triglyceride level was increased in AN-FEP patients (0.7 ± 0.3 and 1.2 ± 0.8 mmol l^{-1} for healthy controls and AN-FEP patients, respectively, $P=5.67\times10^{-5}$, Table 1). When we normalised the data by eliminating the potential influence of triglycerides, the HOMA-IR remained significantly higher in AN-FEP patients when compared to healthy controls (one-way analysis of covariance (ANCOVA) test using triglyceride level as a covariate,$F=5.755$, $df=1$, $P=0.019$).

Table 1
Characteristics of first-episode psychosis (FEP) schizophrenia patients and healthy control volunteers.

	Healthy Control (N=30)	*FEP patients (N=49)*	*t/z/x2 value*	*P value*
Age (years) [a]	26.9 ± 3.9	26.8 ± 8.1	*−0.709*	*0.479*
Male/Female [b]	10/20	14/35	*0.199*	*0.655*
Body mass index (kg/m²) [c]	21.4 ± 2.5	21.6 ± 3.9	*0.213*	*0.832*
Glucose (mmol/L) [c]	5.1 ± 0.4	5.0 ± 0.6	*−0.938*	*0.351*
Insulin (uIU/ml) [a]	4.1 ± 1.9	6.7 ± 3.8	*−3.495*	*0.001*
Cholesterol (mmol/L) [c]	4.3 ± 0.8	4.6 ± 0.9	*1.738*	*0.086*
Triglyceride (mmol/L) [a]	0.7 ± 0.3	1.2 ± 0.8	*−4.026*	*5.67×10^{-5}*
Smoker/Nonsmoker [b]	3/27	7/42	*0.023*	*0.879*

Values are shown as Mean ± S.D. or numbers of participants.

[a] Mann-Whitney U test.
[b] Pearson X^2 test.
[c] Student's t test.