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Leptin/Adiponectin ratio as a potential biomarker for metabolic syndrome in patients with schizophrenia

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ABSTRACT

Objective: Leptin and adiponectin are adipokines which have opposing roles in the development of insulin resistance and metabolic syndrome (MetS). Leptin/adiponectin ratio (L/A ratio) has been proposed as a good biomarker for MetS in general population. This study aimed to compare the strength of association between MetS and leptin, adiponectin and L/A ratio, as well as to assess their performance to diagnose MetS in patients with schizophrenia.

Methods: Patients diagnosed with *DSM-IV* schizophrenia and under clozapine or olanzapine monotherapy for at least six months were recruited. We used the modified ATP III criteria for Asians to evaluate subjects for a diagnosis of MetS.

Results: We recruited 262 study subjects with schizophrenia, and classified them into those with MetS (n = 87) and those without MetS (n = 175). Leptin level was positively correlated with BMI, waist circumference, and insulin level. Adiponectin level was negatively correlated with most metabolic parameters, except glucose level. L/A ratio was positively correlated with most metabolic parameters, except levels of glucose and HDL-C. Significant gender differences existed in leptin levels, adiponectin levels, and L/A ratio. Without and with adjustment of age and gender, binary logistic regression analysis showed that leptin level, adiponectin level, and L/A ratio were significantly associated with MetS. The area under curve (AUC) of L/A ratio and leptin level for MetS was 0.744 (95% CI = 0.685–0.802) and 0.666 (95% CI = 0.601–0.731). The AUC of adiponectin level for the absence of MetS was 0.717 (95% CI = 0.655–0.780). The discriminative strength of L/A ratio for MetS was better in men than in women.

Conclusions: The present study results suggest that L/A ratio may be a preferential marker of metabolic syndrome in patients with schizophrenia compared to leptin or adiponectin alone.

1. Introduction

Schizophrenia is a chronic and debilitating mental illness that affects about 1% of population (van Os and Kapur, 2009). Patients with schizophrenia have a higher medical comorbidity and mortality rate than those in general population (Kredentser et al., 2014; Leucht et al., 2007). The life expectancy of patients with schizophrenia is 10–25 years shorter than that in general population (Laursen, 2011). Cardiovascular disease is a major factor to cause increased mortality in schizophrenia, followed by cancer and infection-related deaths (Nielsen et al., 2013). Considering the mortality, increased rate of physical illness, cognitive and social impairment, schizophrenia has become an important humanistic burden and major public health issue (Millier et al., 2014).

Since the introduction of the second generation antipsychotics (SGAs), those agents have been widely prescribed for the treatment of patients with schizophrenia due to their lower propensity to cause extrapyramidal symptoms and tardive dyskinesia compared to first generation antipsychotics (FGAs). But SGAs present themselves a different set of adverse effects, including weight gain, diabetes mellitus (DM), metabolic syndrome (MetS), and cardiovascular abnormalities (Chen et al., 2011b; Leucht et al., 2013; Muench and Hamer, 2010). Those side

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effects might be delayed to develop for several years after SGA use, and subsequently lead to premature death (Weinmann et al., 2009).

Adipose tissue is now known to be an active and critical endocrine organ (Kershaw and Flier, 2004). It is responsible for the synthesis and secretion of several bioactive molecules termed as adipokines regulating metabolism and inflammation. Two most studied adipokines–adiponectin and leptin–are important in the development of MetS. Adiponectin is an adipocyte-derived plasma protein, and plays important roles in fat and carbohydrate metabolism and the endocrine system (Ouchi et al., 2011). Adiponectin has several bioactive functions, such as anti-diabetic, anti-atherosclerotic, and anti-inflammatory properties (Ryo et al., 2004). Hypoadiponectinemia is closely associated with obesity and MetS (Brooks et al., 2007; Falahi et al., 2015). Among patients with schizophrenia, those with MetS had lower adiponectin levels than those without MetS (Chen et al., 2011a). SGAs can induce insulin resistance (Houseknecht et al., 2007), but the relationship between the use of SGAs and the levels of adiponectin remained uncertain (Bai et al., 2007; Bartoli et al., 2015; Jin et al., 2008; Lu et al., 2015).

Leptin is mainly produced by adipocytes and exerts an anorexigenic effect (Gautron and Elmquist, 2011). Leptin is a mediator of long-term regulation of energy balance (Friedman and Halaas, 1998). Elevated serum leptin levels were correlated with increased food intake, insulin resistance, and other components of the MetS including obesity, hyperlipidemia and hypertension, etc (Ren, 2004). Leptin levels are increased in patients with schizophrenia, especially in those taking SGAs (Jin et al., 2008; Lu et al., 2015; Stubbs et al., 2016). Both preclinical and clinical studies showed that elevated serum leptin levels may precede the antipsychotic-induced body weight gain (Sentissi et al., 2008; Horska et al., 2016). Furthermore, schizophrenia itself might be associated with metabolic abnormality and adipokine dysregulations (Beumer et al., 2012; Harris et al., 2013). The relationships between dysregulated hormonal pathways, SGA treatment, and metabolic abnormality need further investigations.

Cumulative evidences showed that serum levels of leptin and adiponectin are associated with MetS and can be used as diagnostic markers for MetS (Chu et al., 2006; Esteghamati et al., 2011). Recently, leptin/adiponectin ratio (L/A ratio) has been proposed as a better marker of insulin resistance (Oda et al., 2008) and MetS (Falahi et al., 2015; Mirza et al., 2011; Zhuo et al., 2009) than leptin or adiponectin alone. As clozapine and olanzapine among all SGAs have the highest potential to cause metabolic abnormalities and weight gain (Hirsch et al., 2017), their relationship with L/A ratio is worthy of further investigations. In this study, we intended to compare the strength of association between MetS and leptin level, adiponectin level and L/A ratio, as well as to assess their performance to diagnose MetS among a large sample of patients with schizophrenia under clozapine or olanzapine monotherapy.

2. Methods

2.1. Participants and procedure

This study was performed at Taipei Medical University-Wan Fang Hospital and Tsaotun Psychiatric Center in Taiwan. This study was approved by the institutional review board. All participants gave written informed consent. Patients diagnosed with schizophrenia (according to the *DSM-IV* criteria) who received clozapine or olanzapine monotherapy for at least six months were recruited.

2.2. Phenotype measurements

All study participants received clinical interview and anthropometrical parameter assessment, as well as gave fasting blood samples. A trained research nurse interviewed patients to collect demographic and psychiatric information. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres (kg/m^2).

2.3. Laboratory measurement

Blood samples were collected after at least 8 h of fasting. Plasma was stored at −80 °C before measuring the biochemical markers as well as the leptin and adiponectin levels. The serum levels of leptin and adiponectin were measured using ELISA kits (BioVendor Laboratorní medicína a.s, Brno, Czech Republic). Enzymatic colorimetric assays on Roche/Hitachi cobas c systems were used to measure fasting serum levels of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Serum insulin levels were measured using an electrochemiluminescence immunoassay kit (Elecsys Insulin–Roche Diagnostics GmbH, Mannheim, Germany). Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR: fasting glucose [mmol/L]*fasting insulin [mU/L]/22.5) (Matthews et al., 1985).

In this study, we used the modified ATP III criteria for Asians to evaluate subjects for a diagnosis of MetS (Tan et al., 2004). Three of the following five criteria were required: (1) abdominal obesity (waist circumference > 90 cm, in men and > 80 cm, in women); (2) fasting hypertriglyceridemia (≥150 mg/dL or 1.69 mmol/L); (3) low fasting HDL-C levels (≦40 mg/dL or 1.03 mmol/L in men and ≦50 mg/dL or 1.29 mmol/L in women); (4) high blood pressure (≥130/≥85 mm Hg or current treatment with antihypertensive medication); and (5) high fasting plasma glucose levels (≥110 mg/dL or 6.1 mmol/L) or current treatment with antidiabetic medication.

2.4. Statistical analyses

We collected descriptive statistics (mean ± standard deviation, frequency, and percent) of the demographics and biochemical markers as well as the serum levels of leptin and adiponectin. The variables were compared between groups using the Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. We used the Spearman's rank order correlation method to analyze the correlations between various indicators of metabolic parameters. To correct possible errors during multiple comparisons, the modified Bonferroni's method was used (Benjamini et al., 2001). Binary logistic regression analysis was used to assess the independent effects of leptin level, adiponectin level, and L/A ratio on MetS. To quantify the abilities of various indicators to identify MetS, we performed receiver operating characteristic (ROC) analysis. In a ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (1-specificity) for different cut-off points of a parameter. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two groups. Youden index (sensitivity + specificity −1) was calculated to determine the optimal cut-off values for MetS (Youden, 1950). The original value with the maximum of Youden index was considered as the optimal cut-off value. Tests with p values less than 0.05 were considered as statistically significant.

3. Results

3.1. Characteristics of the study subjects

Two hundred and sixty-two subjects with schizophrenia were recruited for the present study. Those study participants were classified into without MetS group (n = 175) and with MetS group (n = 87). The overall prevalence of MetS was 33.2%, with 33.6% in male and 32.8% in female patients, respectively. Table 1 summarized the demographic and metabolic characteristics of study subjects. Compared with the subjects without MetS, the subjects with MetS had significantly longer duration of antipsychotic medication, higher body weight, BMI, waist