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Relationship between inflammation and metabolic syndrome following treatment with paliperidone for schizophrenia

Kyoung-Sae Na [a], Won-Hyoung Kim [b], Han-Yong Jung [a], Seong Gon Ryu [c], Kyung Joon Min [d], Ki-Chang Park [e], Yong-Sik Kim [f], Jin-Sang Yoon [g], Yong Min Ahn [h], Chul-Eung Kim [b,*]

[a] Department of Psychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea
[b] Department of Psychiatry, Inha University Hospital, Incheon, Republic of Korea
[c] Department of Psychiatry, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea
[d] Department of Psychiatry, Chung-Ang University Hospital, Seoul, Republic of Korea
[e] Department of Psychiatry, Wonju Christian Hospital, Wonju, Republic of Korea
[f] Department of Psychiatry, Dongguk University Ilsan Hospital, Ilsan, Republic of Korea
[g] Department of Psychiatry, Chonnam National University, Gwangju, Republic of Korea
[h] Department of Psychiatry, Seoul National University Hospital, Seoul, Republic of Korea

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ABSTRACT

Objective: Metabolic syndrome and antipsychotic medications are associated with inflammation. This study investigated the relationship between inflammation and metabolic syndrome in patients with schizophrenia. It also examined the effects of paliperidone extended release (ER) treatment on metabolic parameters.
Methods: Data were analyzed from schizophrenic patients who participated in a multi-center, open-label, non-comparative clinical trial. Anthropomorphic measurements (*i.e.*, weight, waist circumference, and blood pressure) were assessed along with fasting laboratory values, including white blood cell (WBC) count, glucose, high-density lipoprotein, and triglycerides.
Results: Among the 225 patients at baseline, the group with the highest WBC count displayed a 5.9-fold risk for metabolic syndrome compared with that of the lowest group. An increase of 10^3 WBCs/μL was associated with a 1.4-fold increased risk for metabolic syndrome. After 24 weeks of treatment with paliperidone ER, significant increases were observed in waist circumference and body weight. Changes in WBC count were positively correlated with changes in waist circumference.
Conclusions: Schizophrenic patients with high levels of inflammation should be carefully monitored for metabolic syndrome. Moreover, strategies to reduce inflammation and obesity may prevent metabolic syndrome in patients with schizophrenia who take atypical antipsychotic medication.

1. Introduction

Early mortality rates among patients with schizophrenia are approximately 2–3 times the rate in the general population (Brown et al., 2010; Saha et al., 2007). While unnatural causes such as suicide account for 17% of schizophrenia-related deaths, the vast majority of early mortality in this population is attributable to natural causes, especially cardiovascular disease (Brown et al., 2010). Metabolic abnormalities such as glucose intolerance, obesity, and dyslipidemia are strongly associated with the development and exacerbation of cardiovascular disease (Eckel et al., 2005).

The concept of 'metabolic syndrome' has been proposed to explain the relationships between metabolic abnormalities and cardiovascular disease (Levitt and Lambert, 2002). Metabolic syndrome, also known as syndrome X (Reaven and Chen, 1988) and insulin resistance syndrome (DeFronzo and Ferrannini, 1991), is a constellation of metabolic disturbances encompassing central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol. The prevalence of metabolic syndrome is 15.1–23.7% (Ford et al., 2002; Gu et al., 2005) in the general population and 22.2–60.0% (Kang et al., 2011; McEvoy et al., 2005; Sugawara et al., 2010) in patients with schizophrenia. Several factors, including a sedentary life style, poor diet, low economic status, poor public health, high rates of nicotine and alcohol dependence, and

Abbreviations: ER, extended release; WBC, white blood cell; HDL, high-density lipoprotein; SGA, second-generation antipsychotic; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CRP, C-reactive protein; BMI, body mass index; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, fourth edition; NCEP: ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization; TG, triglyceride.

* Corresponding author at: Department and Research Institute of Psychiatry, Inha University, College of Medicine, 7-206, 3-ga, Shinheung-dong, Jung-gu, Incheon, 400-711, Republic of Korea. Tel.: +82 32 890 3475; fax: +82 32 890 3558.
E-mail address: kce320@inha.ac.kr (C.-E. Kim).

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genetic susceptibility, are associated with the high prevalence of cardiometabolic disturbances in patients with schizophrenia (Ryan and Thakore, 2002).

Antipsychotic medications, particularly second-generation antipsychotics (SGAs), are associated with metabolic syndrome in patients with schizophrenia. Before antipsychotic medications were used to treat schizophrenia, many researchers believed that schizophrenia itself might contribute to an increased vulnerability to the development of metabolic diseases (Ryan and Thakore, 2002). More recently, researchers have suggested that antipsychotics contribute to the development of metabolic syndrome in patients with schizophrenia (Padmavati et al., 2010; Saddichha et al., 2008; Sengupta et al., 2008). This theory was supported by a recent systematic review, which revealed no significant difference in cardiovascular risk between untreated psychotic patients and healthy controls (Foley and Morley, 2011).

Metabolic syndrome is also associated with inflammation. Although inflammatory markers are not included in the diagnostic criteria for metabolic syndrome, inflammation plays an important role in the development of diabetes and atherosclerosis. Moreover, inflammation is believed to be a key pathogenic mechanism for the adverse consequences of metabolic syndrome (Reilly and Rader, 2003; Yaffe et al., 2004).

Individual SGAs have different characteristics. Aripiprazole causes the fewest negative metabolic and inflammatory effects, whereas olanzapine greatly affects metabolic and inflammatory profiles (Weiden, 2007). Previous studies have examined the relationship between metabolic disturbances and inflammatory markers in response to treatment with antipsychotics. Based on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) dataset, Meyer and colleagues reported that changes in C-reactive protein (CRP) and E-selectin correlated with changes in waist circumference, body mass index (BMI), and HDL cholesterol during 3 months of treatment with various antipsychotics (clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine) (Meyer et al., 2009). Fernandez-Egea and colleagues found that abnormal interleukin-6 levels at baseline predicted a significantly greater increase in both total cholesterol and low-density lipoproteins following 12 weeks of treatment with olanzapine (Fernandez-Egea et al., 2011). To date, no reported study has investigated inflammatory and metabolic changes following treatment with paliperidone extended release (ER). Although paliperidone ER is an active metabolite of risperidone (Yang and Plosker, 2007), its metabolic and inflammatory properties may differ from those of risperidone.

This study investigated whether inflammation, determined based on circulating white blood cell (WBC) count, is associated with individual metabolic parameters and the prevalence of metabolic syndrome. It also investigated alterations in inflammatory and metabolic parameters during 24 weeks of treatment with paliperidone ER.

2. Methods

2.1. Subjects

This study involved a *post hoc* analysis of a multi-center, open-label, non-comparative prospective study that was originally designed to examine the subjective effectiveness of switching from antipsychotic medication to paliperidone ER in patients with schizophrenia (ClinicalTrials.gov identifier: NCT00761605; the manuscript has been submitted elsewhere and is currently under review).

The study participants were adult male and female outpatients who met the diagnostic criteria for schizophrenia, as defined in DSM-IV (APA, 1994). The participants ranged in age from 18 to 65 years. They were recruited from 23 study sites in Korea and included patients who were being treated with antipsychotic medication for at least 2 weeks prior to the study screening, and who required a change in antipsychotic medication. The mean (SD) dosage (mg) for each prior antipsychotic was as follows: risperidone 4.65 (2.23), olanzapine 14.17 (5.54), aripiprazole 19.75 (8.54), amisulpride 563.64 (280.26), quetiapine 532.50 (304.61), and ziprasidone 106.67 (40.00). Exclusion criteria were: a history of neuroleptic malignant syndrome, a risk for suicide or aggressive behavior, a severe preexisting gastrointestinal narrowing or inability to swallow the medication whole, pregnancy or breastfeeding, participation in any investigational drug trial within 1 month prior to the screening visit, a history of treatment with a long-acting injectable antipsychotic or clozapine prior to the screening visit, a history of allergic reaction to risperidone or paliperidone, current substance abuse or dependence, and a history of substance abuse or dependence within the past 6 months. Permission and informed consent were obtained from all subjects, and then the antipsychotic medication histories were gathered from patients' medical records. Medical comorbidity, including diabetes and cardiovascular diseases, and other personal data were obtained from self-reported questionnaires, laboratory results, and medical records when available.

2.2. Procedures

During the 24-week study period, a flexible dose of paliperidone ER (range: 3–12 mg) was administered daily to all participants. Clinicians were allowed to use their preference for medication switching strategies, including an abrupt switch, a taper switch, or a cross-taper switch. Vital signs (*i.e.*, weight, blood pressure, and pulse rate) were assessed at baseline and at every visit during the 24-week study period. Waist circumference was assessed at baseline using a tape measure at the level of the naval with minimal respiration, and was also assessed at the end of the 24-week period. Fasting laboratory tests (*i.e.*, WBC count and metabolic parameters) were assessed at baseline and 24 weeks. All blood samples were drawn after 8 h of overnight fasting.

The study was performed in accordance with the Declaration of Helsinki and was approved by each institutional review board. After a full explanation of the study, written informed consent was obtained from all subjects.

2.3. Definition of metabolic syndrome

Metabolic syndrome and its components were defined according to the modified version of the National Cholesterol Education Program Adult Treatment Panel III (NCEP: ATP III) for Asian populations (Heng et al., 2006; NCEP Expert Panel, 2002; WHO Western Pacific Region, 2000). Based on this definition, participants were classified as having metabolic syndrome when any three of the following were present: waist circumference $\geq$90 cm in males or $\geq$80 cm in females; fasting triglycerides $\geq$150 mg/dL; blood pressure $\geq$130/85 mm Hg or hypertensive on medication; HDL $<$40 mg/dL in males or $<$50 mg/dL in females; and fasting glucose $>$100 mg/dL. Note that the original cut-off value for waist circumference was 102 cm in males and 88 cm for females Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (2001); we believed that these cut-off values were too high and would result in an underestimation of obesity in an Asian population. Therefore, we used the waist circumference cut-off points of 90 cm for males and 80 cm for females according to the modified version of the NCEP: ATP III for Asian populations.

2.4. Statistical analysis

Descriptive statistics were used to analyze the baseline subject demographic and clinical data. Pearson's partial coefficient adjusted for age and gender was used to examine the relationships between WBC count and metabolic parameters. In the correlation analysis, WBC count was log-transformed due to its highly skewed distribution.