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Total and differential white blood cell counts, inflammatory markers, adipokines, and the metabolic syndrome in phase 1 of the clinical antipsychotic trials of intervention effectiveness study

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ABSTRACT

Objective: The metabolic syndrome is highly prevalent in patients with schizophrenia, and is associated with a state of chronic, low-grade inflammation. We investigated relationships between total and differential white blood cell (WBC) counts, inflammatory markers, adipokines and the metabolic syndrome in patients with schizophrenia.

Method: For subjects with available data from the baseline/screening visit of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, WBC counts, inflammatory markers, and adipokines were investigated as predictors of the metabolic syndrome (and its components), using linear and binary logistic regression models, controlling for potential confounding effects of age, sex, race, smoking, fasting status, alcohol, and illicit drug use.

Results: After controlling for potential confounders, blood CRP, interleukin-6, and leptin were significant predictors of all five individual components of the metabolic syndrome (as both continuous and categorical outcome measures). Furthermore, total WBC (OR = 2.31, 95% CI 1.58–3.41, $p < 0.01$) and lymphocyte (OR = 2.51, 95% CI 1.75–3.60, $p < 0.01$) counts were the strongest predictors of current metabolic syndrome.

Conclusions: Our findings provide the strongest evidence to date that measurement of total and differential WBC counts are germane to the clinical care of patients with schizophrenia, and that inflammation and adipokines are associated with metabolic disturbance in these patients.

1. Introduction

The metabolic syndrome is a constellation of metabolic risk factors associated with the development of atherosclerotic cardiovascular disease (Galassi et al., 2006; Grundy et al., 2005) and cardiovascular disease mortality (Galassi et al., 2006) — the leading cause of death in patients with schizophrenia (Saha et al., 2007). The metabolic syndrome is common in patients with schizophrenia, with a prevalence of 43% — based on American Heart Association criteria (Grundy et al., 2005) — in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; McEvoy et al., 2005).

The metabolic syndrome is also associated with a state of chronic, low-grade inflammation (Devaraj et al., 2010). A meta-analysis found that high-sensitivity CRP (hsCRP) was an independent predictor of cardiovascular disease (Kaptoge et al., 2010). Schizophrenia is also associated with increased inflammation, including aberrant blood levels of pro-inflammatory cytokines (Miller et al., 2011), lymphocytes (Miller et al., 2013a) and CRP (Miller et al., 2014), including studies in patients with first-episode psychosis and minimal exposure to antipsychotics. The adverse metabolic effects of atypical antipsychotics, which increase metabolic syndrome risk, may potentiate aberrant blood levels of inflammatory markers (Beumer et al., 2012).

Several large population-based samples found that total and differential white blood cell (WBC) counts were associated with metabolic syndrome risk and individual metabolic syndrome criteria (Kim et al., 2008; Lao et al., 2008). Within schizophrenia, one study found that higher total WBC counts are associated with increased risk of the metabolic syndrome and more severe psychopathology (Fan et al., 2010). We previously found that total WBC count, monocytes, and hsCRP were significant predictors of metabolic syndrome in patients with schizophrenia, and hsCRP was also a significant predictor of increased waist circumference and triglycerides (Miller et al., 2013b). In a subsequent study, we found that total WBC count was a significant predictor of an elevated 10-year estimated risk of myocardial infraction and cardiovascular disease, using Framingham risk scores (Miller et al., 2015).

In the CATIE study, effects of antipsychotics on changes in blood CRP, E-Selectin, intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) levels between screening and 3 months have been previously reported (Meyer et al., 2009). At 3 months, median CRP and E-Selectin levels were significantly greater in patients with

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versus without metabolic syndrome. Furthermore, median CRP, E-Selectin, and ICAM-1 levels were significantly greater for subjects positive (versus negative) for some individual metabolic syndrome criteria. However, this study focused on changes in inflammatory markers over time, and thus included a smaller subset of subjects in the CATIE study with available blood samples at multiple time points, explored categorical, but not continuous, relationships between inflammatory markers and components of the metabolic syndrome, and did not investigate relationships between total and differential WBC counts and the metabolic syndrome.

The purpose of this study is to investigate the relationship between total and differential WBC counts, inflammatory markers, and the metabolic syndrome in a large sample of patients with schizophrenia from the CATIE study. We hypothesize that total and differential WBC counts, as well as inflammatory markers, are associated with metabolic syndrome risk and individual metabolic syndrome criteria in these subjects. We also explore which of these blood markers is the strongest predictor of current metabolic abnormalities.

2. Material and methods

Data were obtained from the publicly available limited access CATIE schizophrenia trial dataset. A full description of the CATIE schizophrenia trial has been previously described (Lieberman et al., 2005). The study was deemed exempt by the Georgia Regents University IRB. Blood for total and differential WBC, inflammatory markers (CRP, interleukin-6 [IL-6], E-Selectin, ICAM-1, and VCAM-1), and adipokines (adiponectin and leptin) were collected at baseline/screening. Plasma was CRP levels were determined using a single enzyme-linked immunosorbent assay (ELISA). Plasma levels of all other inflammatory markers and adipokines were measured using a multiplex ELISA, which enables simultaneous quantification of a panel of markers from a single blood sample. Details on assay methodology have been described elsewhere (Meyer et al., 2009). Complete blood counts with differential, blood glucose, and lipid panels were analyzed by standard clinical laboratory assays. Vital signs and anthropometric measures, including height, weight, and waist circumference were also obtained at baseline/screening. We excluded subjects currently taking scheduled non-steroidal anti-inflammatory, corticosteroids, or other immunomodulatory agents. Data on covariates, including age, sex, race, smoking (number of cigarettes/day in the past week), alcohol and illicit drug use (based on the Clinician Alcohol Use Scale and the Clinician Drug Use Scale), and whether the subject was fasting at the time of blood draw were also available.

Metabolic syndrome was defined as per the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (Grundy et al., 2005). Subjects meeting three or more of the following five criteria were defined as having the metabolic syndrome: 1) waist circumference ≥ 102 cm in males or ≥88 cm in females, 2) fasting triglycerides ≥150 mg/dL, 3) fasting HDL <40 mg/dL in males or <50 mg/dL in females, 4) blood pressure ≥ 130/85 mm Hg or on antihypertensive drug treatment in a subject with a history of hypertension, 5) fasting glucose ≥100 mg/dL or on drug treatment for elevated glucose.

The data were analyzed using SPSS version 22 (SPSS, Inc.; Chicago, Illinois). Subjects were stratified based on the presence or absence of the metabolic syndrome. Demographic and blood marker analyses in subjects with and without the metabolic syndrome were analyzed using either Student's t-test (2-sided), Mann–Whitney U, or Fisher's exact test (2-sided). A one-sample Kolmogorov–Smirnov test was used to examine each variable for normality. All of the blood markers (total and differential WBC, inflammatory markers, and adipokines) as well as all of the individual components of the metabolic syndrome were not normally distributed, and were log transformed prior to the analyses. Binary correlation coefficients (Spearman's rho) were calculated between blood markers, metabolic syndrome variables, and other demographic and clinical variables. Linear regression models were used to evaluate blood markers as predictors of each component of the metabolic syndrome, after controlling for potential confounding effects of age, sex, race, smoking, fasting status, alcohol and illicit drug use. Binary logistic regression models were used to evaluate blood markers as predictors of the metabolic syndrome and individual metabolic syndrome criteria, after controlling for the same potential confounding factors. For all analyses, results were considered statistically significant at the $\alpha = 0.05$ level (two-sided).

3. Results

Table 1 presents the demographic and clinical characteristics of the study sample. The number of subjects with available data on blood markers ranged from 1194 (for adiponectin) to 1416 (for ICAM-1), with a mean of 1363 subjects per marker. Data on smoking were available for 1401 subjects, alcohol and drug use for 1439 subjects, and fasting status for 1357 subjects.

Table 1
Demographic and laboratory characteristics of the study sample.

Variable	Subjects		p-Value[a]
	Metabolic syndrome		
	Yes (n = 551)	No (n = 899)	
	Mean (SD)	Mean (SD)	
Age	41.7 (10.5)	39.9 (11.5)	<0.01
Smoking (cigarettes/day)	12.7 (15.4)	12.3 (13.8)	0.58
WBC ($\times 10^3/\mu L$)	7.7 (2.5)	7.0 (2.3)	<0.01
Neutrophils ($\times 10^3/\mu L$)	4.8 (2.0)	4.3 (1.9)	<0.01
Lymphocytes ($\times 10^3/\mu L$)	2.2 (0.8)	2.0 (0.7)	<0.01
Monocytes ($\times 10^3/\mu L$)	0.48 (0.20)	0.45 (0.19)	<0.01
E-Selectin (pg/mL)	30,965 (27,053)	27,037 (27,755)	0.01
VCAM (pg/mL)	1,064,555 (477,513)	1,046,139 (498,610)	0.36
ICAM-1 (pg/mL)	353,301 (373,125)	333,133 (300,034)	0.03
Adiponectin (pg/mL)	10,967,438 (5,426,266)	13,659,044 (9,228,877)	<0.01
CRP (pg/mL)	1,593,543 (5,174,203)	13,659,044 (4,458,161)	0.03
IL-6 (pg/mL)	125.2 (182.3)	91.0 (155.1)	<0.01
Leptin (pg/mL)	2125 (1528)	1328 (1516)	<0.01
	n (%)	n (%)	p-Value[b]
Sex			<0.01
Male	378 (35.1)	699 (64.9)	
Female	173 (46.4)	200 (53.6)	
Fasting (yes)	262 (37.9)	430 (62.1)	0.47
Race			<0.01
White	379 (43.5)	492 (56.5)	
Black	144 (28.2)	366 (71.8)	
Native American	10 (37.0)	17 (63.0)	
Asian	14 (41.2)	20 (58.8)	
Pacific Islander	4 (50.0)	4 (50.0)	
Alcohol Use			0.01
Abstinent	378 (40.5)	555 (59.5)	
Use without impairment	137 (34.5)	260 (65.5)	
Abuse or dependence	29 (26.6)	80 (73.4)	
Drug use			0.01
Abstinent	439 (40.2)	654 (59.8)	
Use without impairment	63 (30.3)	145 (69.7)	
Abuse or dependence	42 (30.4)	96 (69.6)	

[a] Mann–Whitney U test was used for all comparisons, except age, which was analyzed using Student's t-test, 2-sided.
[b] Fisher's Exact Test, 2-sided was used for all comparisons.