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ORIGINAL PAPER

Correlations between Body Mass Index, Plasma High-Sensitivity C-Reactive Protein and Lipids in Patients with Schizophrenia

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Abstract
High prevalence of obesity in individuals with schizophrenia, associated with metabolic syndrome, leads to high rate of premature deaths from cardiovascular disease (CVD) in this population. Body mass index (BMI) and C-reactive protein (CRP) are correlated in the general population but this relationship has not been fully elucidated in patients with schizophrenia. We aimed to evaluate the correlation between BMI and CRP while relating both variables to plasma lipids in patients with schizophrenia. BMI, fasting high sensitivity CRP (hs-CRP), cotinine, and lipids were measured in 106 patients with schizophrenia (diagnosis confirmed with MINI). Pearson's and partial correlations (adjusting for age, sex, race, education and cotinine) between BMI, hs-CRP and lipids were calculated. Based on BMI, the patients were divided into normal-weight vs. overweight/obese and t-tests and linear regression were done to compare hs-CRP and lipids in the 2 groups. BMI positively correlated with hs-CRP ($r = 0.29$, $p = 0.004$). BMI and hs-CRP negatively correlated with HDL in the total sample ($r = -0.29$, $p = 0.004$; $r = -0.37$, $p < 0.001$ respectively). Furthermore, hs-CRP negatively correlated with HDL in overweight/obese patients ($r = -0.41$, $p = 0.003$), but not in normal-weight patients. hs-CRP and triglycerides were higher (1.62 ± 0.09 mg/L vs. 0.56 ± 0.08 mg/L, $p < 0.001$; 121.77 ± 8.96 mg/dL vs. 91.23 ± 6.52 mg/dL, $p = 0.008$ respectively) and HDL lower (39.55 ± 1.48 mg/dL vs. 50.68 ± 2.24 mg/dL, $p < 0.001$) in overweight/obese patients. Being overweight/obese is associated with increased inflammation and dyslipidemia in patients with schizophrenia. Effective interventions to prevent weight gain in schizophrenia are urgently needed.

Keywords Schizophrenia · BMI · Hs-CRP · Plasma lipids · Overweight · Obese · Cardiovascular disease

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Introduction

Schizophrenia, a severe mental illness with a complex inflammatory pathophysiology [1–3], is associated with increased body mass index (BMI) [4–6]. Relevant factors that contribute to elevated BMI in schizophrenia include sedentary life style, negative symptoms [7], atypical antipsychotic administration [8–13], impaired peripheral glucose metabolism associated with disease pathophysiology [14], and poor dietary habits [15]. Elevated BMI in schizophrenia is also related to a high rate of metabolic syndrome (MetS) which contributes to a disproportionately increased rate of death and other adverse sequelae from cardiovascular disease (CVD) among individuals with the illness [16–18]. Blood C-reactive protein (CRP), an acute-phase plasma protein, is also elevated in patients with schizophrenia relative to healthy controls [19, 20], and this finding is thought to be a reflection of immune dysregulation associated with the illness [1, 21, 22]. Furthermore, elevated CRP has been linked to several adverse outcomes including negative [23], cognitive [24] and depressive symptoms [24], as well as all-cause mortality [25], aggression [26] and impaired functional physical capacity [27] in patients with schizophrenia.

BMI and CRP levels are positively correlated in the general (non-psychiatric) population [28–30], and the elevated CRP levels seen in individuals with abnormal BMI (overweight/obese) is reported to be due to a state of low-grade systemic inflammation present in overweight and obese persons [31]. Obesity-induced inflammation has also been suggested to bear a pathophysiologic link between obesity, Insulin resistance/type-2 diabetes [31], and CVD [32]. Moreover, elevated CRP is thought to independently predict adverse cardiovascular sequelae in the setting of metabolic syndrome [33], and CRP is considered to be a biomarker of cardiovascular risk [34]. Combining CRP with BMI in cardiovascular risk assessment/prediction models could enhance the predictive accuracy of such models [33, 35, 36].

Despite the high rate of CVD and deaths from CVD in schizophrenia, there is a paucity of studies that have directly evaluated the association of BMI with CRP while also relating both variables to dyslipidemia (a well-documented risk factor for CVD) in patients with schizophrenia. In two separate studies of patients with schizophrenia, high-sensitivity CRP (hs-CRP) correlated with BMI [37, 38] but hs-CRP also correlated with plasma triglycerides in one of the two studies [38]. In two other independent studies that employed waist circumference as an additional measure of overweight/obesity status, CRP positively correlated with waist circumference [39, 40]; however, CRP also correlated with BMI and waist/hip ratio in one of the two studies [40], although the strength of the correlation was weakest for BMI. One study of patients with schizophrenia failed to detect an association between hs-CRP and BMI, although hs-CRP correlated with waist/hip ratio in the study [41]. A fairly recent meta-regression analyses also indicated that BMI and CRP are correlated in patients with schizophrenia but there was no association between CRP and waist circumference or waist/hip ratio in the meta-regression analyses [21].

To foster the elucidation of the relationship between BMI and CRP in schizophrenia, we have examined the correlation of BMI and plasma hs-CRP levels, while also relating both variables to plasma lipids and controlling for several potential confounders in a robust sample of patients with schizophrenia. We hypothesized that BMI and hs-CRP will be positively correlated and that both will also be associated with dyslipidemia.

Methods

Patient Sample

106 patients with schizophrenia were recruited during a period of inpatient treatment for exacerbation of psychosis. The diagnosis of schizophrenia was confirmed with the Mini-International Neuropsychiatric interview (MINI), version 5 [42] and all the patients were receiving antipsychotic medication at the time of enrollment. Demographic information was obtained (age, sex, race, level of education) as well as plasma cotinine levels (a metabolite of nicotine). Inclusion criteria for this study were: (1) age 18 to 60 years; (2) prior documented diagnosis of schizophrenia by DSM-5 criteria, and; (3) negative urine pregnancy test for female patients. Exclusion criteria were: (1) current endorsement of suicidal or homicidal ideations; (2) prior diagnosis of primary cognitive disorder; (3) any current infectious diagnosis or primary inflammatory condition; (4) any current use of corticosteroids or non-steroidal anti-inflammatory medications; (5) any recent or current use of warfarin or anticoagulant medications, and; (6) urine drug screen positive for psychostimulant drugs.

The study was approved by the institutional review board and completed in conformity with the latest version of the Declaration of Helsinki. All the participants completed a written informed consent form after the study was described to them and they demonstrated an understanding of the study procedures.

BMI, Hs-CRP, Cotinine and Plasma Lipid Measurements

A scale with a mechanical height rod was used to measure each participant's weight and height. BMI was calculated by dividing each participant's weight (in kilograms) by the square of the height (in meters). After fasting overnight, venous blood was collected (between 6 and 7 am) from all the participants; plasma was isolated and stored at −80 °C until analyzed. Plasma hs-CRP was measured using Human high sensitivity C-reactive protein ELISA (MyBioSource, MBS703598) according to the manufacturer's instructions. Samples were diluted 1:1000. Plasma cotinine was determined using Liquid chromatography–mass spectrometry. Plasma total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured by Quest Diagnostics (Secaucus, NJ) using spectrophotometry [43]. Non-HDL Cholesterol was measured by subtracting HDL from TC. Non-HDL cholesterol is increasingly considered to be a more comprehensive index of cardiovascular risk especially if measured in the non-fasting state [44].

Statistical Analyses

Descriptive statistics are presented as means ± standard deviation (SD) and percentages as appropriate. The distribution of hs-CRP and cotinine were skewed to the right and these variables were therefore log-transformed (base 10); log-hsCRP and log-cotinine were used in all subsequent analyses. Geometric means obtained by exponentiating the mean log-transformed values, are presented for both hs-CRP and cotinine. To evaluate the linear association of BMI with hs-CRP (primary analysis), Pearson correlations were calculated while partial correlations were used to control for age, sex, race, education and plasma cotinine. Secondary analyses included evaluation of Pearson's and partial correlations between hs-CRP, BMI and plasma lipids. The patient sample was also divided into two groups namely, normal-weight (BMI between 18.5–25)

and overweight/obese (BMI above 25). T-test was used to compare hs-CRP and plasma lipids between the 2 groups and regression analyses used to control for potential confounding variables (age, sex, race, education and plasma cotinine). The correlation of BMI and hs-CRP with plasma lipids was also separately evaluated in the 2 groups. To control for type 2 error, statistical significance was set at 0.01 and all tests were two-tailed. Data analyses was performed using IBM SPSS version 24 (IBM Corp., Armonk, NY, USA).

Results

Demographics

The demographic and clinical characteristics of the sample are depicted in Table 1. The sample was relatively young (mean age 32.9 ± 12.28 years), consisted of more men relative to women (71.6% vs. 28.4%), and was predominantly African American (51.9%). 91.6% of the study participants had obtained less than 2 years college attendance. The mean weight of the sample was in the overweight range.

Correlation of BMI with Hs-CRP

BMI and hs-CRP were positively correlated ($r = 0.29$, $p = 0.004$) and this correlation persisted after controlling for age, sex, race, education, and cotinine levels (partial $r = 0.31$, $p = 0.003$) (Table 2).

Table 1 Demographic and clinical variables of 106 patients with Schizophrenia

Demographic and clinical variables	Value
Mean age ± SD	32.90 ± 12.28
Sex	
Male n (%)	76 (71.6%)
Female n (%)	30 (28.4%)
Race	
Caucasian n (%)	33 (31.1%)
African American (%)	55 (51.9%)
Hispanic n (%)	16 (15.1%)
Asian n (%)	2 (1.9%)
Education Level	
No high-school graduation n (%)	34 (32.1%)
Graduated high-school (or equivalent) n (%)	38 (35.9%)
Part college n (%)	25 (23.6%)
Graduated >2 years of college n (%)	9 (8.4%)
BMI Status	
Normal weight n (%)	47 (46.5)*
Obese/overweight n (%)	54 (53.5)*
Mean BMI ± SD	26.99 ± 7.03
Geometric mean hs-CRP ± SD (mg/L)	1.05 ± 0.62
Geometric mean cotinine level ± SD (ng/ml)	15.14 ± 0.72
Mean Total Cholesterol ± SD (mg/dL)	157.53 ± 32.05
Mean Triglycerides ± SD (mg/dL)	106.59 ± 56.893
Mean LDL ± SD (mg/dL)	91.46 ± 29.89
Mean non-HDL Cholesterol ± SD (mg/dL)	112.78 ± 35.27
Mean HDL ± SD (mg/dL)	44.75 ± 14.40

Geometric means are based on back-transformed means of log transformed values

SD standard deviation; *BMI* Body mass index; *hs-CRP* high-sensitivity C-reactive protein

*5 participants had missing data on BMI

Correlation of Hs-CRP and BMI with Plasma Lipids

hs-CRP correlated negatively with HDL ($r = -0.37$, $p < 0.001$) in the entire sample, a finding that persisted after controlling for the confounding variables (Table 2). In the sub-group analyses, hs-CRP correlated negatively with HDL in the overweight/obese patients ($r = -0.41$, $p = 0.003$), and this result persisted after controlling for confounding variables. However, hs-CRP did not correlate with any of the plasma lipids in the normal-weight patients. In the total sample, BMI negatively correlated with HDL ($r = -0.29$, $p = 0.004$) and this finding resisted adjustment for confounders (Table 2). BMI did not correlate with any of the plasma lipids in the subgroup analyses (normal-weight and overweight/obese patients).

Comparison of Hs-CRP and Plasma Lipids in Normal-Weight Vs. Overweight/Obese Patients

Plasma hs-CRP was significantly higher in the overweight/obese sub-group compared to the normal-weight patients (geometric mean 1.62 ± 0.09 mg/L vs. 0.56 ± 0.08 mg/L, $p < 0.001$) (Fig. 1a). Plasma TG was significantly higher (121.77 ± 8.96 mg/dL vs. 91.23 ± 6.52 mg/dL, $p = 0.008$) and HDL was significantly lower (39.55 ± 1.48 mg/dL vs. 50.68 ± 2.24 mg/dL, $p < 0.001$) in the overweight/obese patients relative to normal-weight patients Fig. 1b. The statistical significance of these findings persisted after controlling for age, race, gender, plasma cotinine, and education.

Discussion

In our sample of patients with schizophrenia, BMI positively correlated with plasma hs-CRP, a finding that was independent of age, sex, race, education or cotinine (a metabolite of nicotine) levels. hs-CRP also negatively correlated with HDL in the total sample and in the overweight/obese patients but this association was not observed in the normal-weight patients. BMI negatively correlated with HDL only in the total sample. Inflammation (as indicated by hs-CRP) and dyslipidemia (elevated TG and reduced HDL) were associated with the overweight/obese patients, indicating worsening cardiovascular status and risk for future development of

Table 2 Correlation of hs-CRP with BMI and plasma lipids before and after adjustment for age, sex, race, education, and cotinine levels

	Pearson's correlation coefficient (unadjusted) hs-CRP	p value	Pearson's correlation coefficient (adjusted) hs-CRP	p value	Pearson's correlation coefficient (unadjusted BMI	p value	Pearson's correlation coefficient (adjusted BMI	p value
BMI	**0.29**	**0.004**	**0.31**	**0.003**				
Total cholesterol	−0.09	0.397	−0.08	0.442	−0.09	0.376	−0.11	0.503
Triglycerides	0.04	0.709	0.01	0.908	0.06	0.562	0.12	0.467
LDL	0.03	0.777	0.02	0.877	−0.01	0.987	0.01	0.966
Non-HDL cholesterol	0.08	0.445	0.02	0.887	0.04	0.733	0.05	0.751
HDL	**−0.37**	**<0.001**	**−0.36**	**<0.001**	**−0.29**	**0.004**	**−0.41**	**0.009**

Bold entries indicate statistically significant correlations, partial correlations and p-values

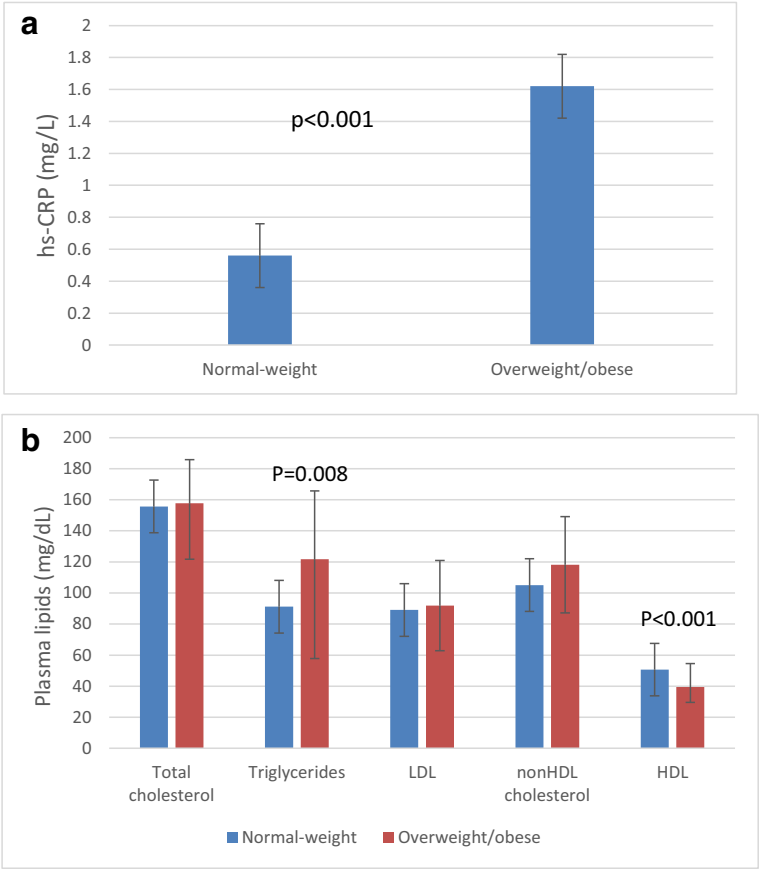

Fig. 1 **a.** Comparison of plasma high sensitivity C-reactive protein (hs-CRP) in normal-weight and overweight/obese patients with schizophrenia **b**. Comparison of plasma lipids in normal-weight and overweight/obese patients with schizophrenia

metabolic syndrome. Our results are consistent with the few available studies on the association of BMI with CRP in schizophrenia [37–40].

Inflammation appears to play a key pathophysiologic role in obesity [28–31] and in schizophrenia [1–3, 22, 45], and the relationship is complex and multifactorial. CRP is regarded as a biomarker of cardiovascular disease and a predictor of future cardiovascular events, especially in the setting of metabolic syndrome [33]. The correlation of hs-CRP with dyslipidemia, especially with low HDL levels as affirmed by our study is consistent with findings in non-psychiatric samples [33]. CRP has been proposed to be a state marker (i.e. might be related to severity of psychosis) in schizophrenia [1, 3], and there is evidence that patients with schizophrenia may be predisposed to obesity and metabolic syndrome [4–6]; while metabolic syndrome occurs in up to a third of the general population [46], it exists in up to 45% of patients with schizophrenia [47], likely due to medication effects as well as immune dysregulation and upregulation of pro-inflammatory cytokines [48]. In a study of first-episode schizophrenia spectrum disorders, cardiometabolic abnormalities, including dyslipidemia and metabolic syndrome, were present early in the course of the disease [49].

Our study supports the theory that elevated CRP correlates with worsening metabolic status in schizophrenia. CRP, which was elevated in the overweight/obese patients in this study, is

likely one of many dysregulated inflammatory mediators that contribute to a pro-inflammatory response by the immune system and ultimately lead to metabolic syndrome [48]. Obesity significantly affects life expectancy in the setting of schizophrenia and increases the risk for negative cardiovascular outcomes [16, 17]. The standardized mortality rate for schizophrenia in many countries is 2.5, and patients with schizophrenia die 15–20 years earlier than the general population, most often due to cardiovascular sequelae [16, 50, 51]. Cardiovascular disease in individuals with metabolic syndrome may be related to post-prandial activation of "foamy" monocytes, a phenomenon in which lipid-laden monocytes are activated by adipokines and triglyceride-rich lipoproteins, becoming highly adhesive via increased expression of CD11c integrin and migrating into the vascular endothelium, thereby generating atherosclerosis and potentially atherothrombosis [33, 52, 53].

Importantly, many common pharmacologic treatments for schizophrenia, especially atypical antipsychotics, lead to increased BMI and risk for metabolic syndrome [8–10, 13]. Proposed mechanisms for this development include downregulation of genes involved in the mitochondrial electron transport chain [54], predisposition of patient genetics relating to insulin pathways [13], and increased appetite [8]. Specifically, metabolic impairment has been most commonly documented with the administration of clozapine and olanzapine, although increase in BMI and metabolic syndrome have also been observed with administration of other antipsychotics to relatively lesser degrees [12]. However, it is worth mentioning that clozapine, the antipsychotic medication with the highest liability for BMI elevation and metabolic syndrome, is the most effective and is also the only antipsychotic medication approved for treatment-resistant psychosis. Olanzapine (in comparison with 4 other non-clozapine antipsychotics) was also the most effective in the CATIE (Clinical Antipsychotic Trial of Intervention Effectiveness) trial [55], a landmark pragmatic clinical trial. Elucidating the underlying mechanisms of antipsychotic-induced weight gain and metabolic syndrome is therefore a high priority area of research as it could lead to novel treatments and strategies to prevent metabolic syndrome-related morbidity and mortality in this patient population.

The strengths of this study include the robust sample size, adjustments for several confounding variables including smoking (cotinine) which is related to inflammation, exclusion of patients with overt inflammatory disease which could raise CRP levels, and blood draw after overnight fasting. The diagnosis of schizophrenia was also confirmed with a structured interview. This study is however limited by its cross-sectional design which precludes us from making causal inferences. We also do not have data on the specific antipsychotic medication(s) and other psychotropic medications as well as duration of treatment for each patient; it is however important to mention the fact that hs-CRP and BMI have been correlated in medication-free patients [40] and even though CRP is increased in schizophrenia, its level is not altered by antipsychotics [21]. Another limitation is the absence of data on childhood maltreatment which has been shown to be associated with elevated CRP and BMI in patients with schizophrenia and bipolar disorder [56].

In conclusion, our study suggests that overweight/obesity status in schizophrenia is associated with increased inflammation and dyslipidemia. CRP is already thought to represent an excellent predictor of future cardiovascular events in the setting of metabolic syndrome [33]; the utility of hs-CRP as a biomarker of adverse metabolic status and risk assessment for prevention of adverse sequelae and improvement of outcomes in schizophrenia is underscored by this study and should continue to be evaluated in future studies. Future longitudinal studies should also evaluate potential gender and racial differences in risk of developing metabolic syndrome and the underlying mechanisms in patients with schizophrenia. The potential utility of interventions that can reduce CRP levels should also be evaluated prospectively. The identification of other biomarkers of cardiovascular risk which could be combined with CRP

could foster the development of a personalized medicine approach in the overall care of patients with schizophrenia.

Compliance with Ethical Standards

Conflicts of Interest There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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