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REPORT

Smoking and Serum Lipid Profiles in Schizophrenia

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Abstract Schizophrenia is associated with a high prevalence of cigarette-smoking and abnormal lipid profiles. The purpose of this study was to determine whether the profiles differ between schizophrenic smokers and non-smokers and whether the lipid profiles are related to psychopathological symptoms. Serum lipid profiles were measured in 130 male inpatients with DSM-IV-defined schizophrenia: 104 smokers and 26 non-smokers. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Our results showed that positive PANSS symptoms were fewer in smokers than in non-smokers, while the negative symptoms were fewer in those who smoked more cigarettes. Total protein and globulin levels were significantly lower in the smokers than in the non-smokers. However, there was no significant difference in total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol, apolipoprotein A1, or apolipoprotein B between the smokers and non-smokers. However, the PANSS positive subscale had a significant negative correlation with the HDL-c levels (a protective factor) in the smokers but not in the non-smokers. Our findings suggest that schizophrenic patients who smoke have fewer psychotic symptoms, but contrary to expectation, smoking does not alter lipid profile levels.

Keywords Schizophrenia · Nicotine · Cigarette smoking · Lipid profiles · Symptoms

Introduction

The prevalence of smoking is greater in patients with schizophrenia than in the general population and in other mentally-ill patients [1–4]. A meta-analysis of worldwide smoking studies demonstrated a higher rate of smoking in patients with schizophrenia than in general population [1]. Smokers with schizophrenia are more likely to be heavy smokers and extract more nicotine from their cigarettes than normal smokers [5]. The reasons for this higher prevalence of smoking in patients with schizophrenia are still unclear. Possible reasons include attempts to reduce the negative symptoms and the side-effects of antipsychotic drugs or improving the cognitive deficits in schizophrenia [6–8].

Many studies have reported that patients with schizophrenia have significantly altered lipid profiles, particularly those treated with second-generation antipsychotic drugs (e.g. clozapine and olanzapine) [9–12]. These altered profiles contribute to an increased risk of metabolic syndrome, obesity, diabetes, and cardiovascular disease. Moreover, a recent study has reported abnormal lipid profiles and glycometabolic parameters in drug-naïve, first-episode schizophrenic patients compared to healthy

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controls [13]. This suggests that lipid metabolism is abnormal in schizophrenic patients before the commencement of antipsychotic drug treatment.

It is well-known that smoking alters serum lipid profiles, as characterized by increased total cholesterol (TC), triglycerides (TG), ApoB/ApoA1 ratio, and low-density lipoprotein cholesterol (LDL-c), along with decreased high-density lipoprotein cholesterol (HDL-c) [14–16]. However, the mechanisms by which smoking changes serum lipid and lipoprotein levels are still unknown. One possible explanation is that nicotine stimulates the secretion of catecholamines, cortisol, and growth hormones, and increases the serum concentration of free fatty acids, which in turn stimulates the hepatic secretion of very-low-density lipoprotein and triglycerides [17]. Also, smoking modifies serum lipid profiles in a pro-atherogenic manner [18].

Given the higher smoking rates in schizophrenic patients and the close relationship between smoking and abnormal lipid metabolism, we hypothesized that the higher smoking rates in schizophrenic patients could cause deterioration of the lipid profiles. However, to our knowledge, no published studies have investigated the effect of smoking on serum lipid profiles in schizophrenic patients.

As smoking is very infrequent among women in China (61% men and 4% women), and because of the gender differences in smoking behaviors, we included only male participants [19]. We therefore compared the lipid profiles in male smokers and non-smokers with schizophrenia and determined whether there is any relationship between the profiles and psychopathological symptoms in these patients.

Participants and Methods

Participants

A total of 130 male in-patients were recruited from Beijing Hui-Long-Guan Hospital. The recruitment criteria were: (1) diagnosis of schizophrenia according to the Structured Clinical Interview of DSM-IV (SCID); (2) chronic illness (at least 5 years in duration); (3) between 26 and 65 years old; (4) Han Chinese; and (5) treated with stable doses of oral antipsychotics for at least 12 months before the start of the study.

A detailed smoking questionnaire was used to collect detailed information, including the average number of cigarettes per day in the week before entry into the study. If a participant identified himself as a current non-smoker but had previously smoked, he was regarded as a quitter and excluded from the study. Based on the questionnaire responses, we identified 104 participants as 'smokers' and 26 as 'non-smokers'.

All participants had a complete medical history, physical examination, and laboratory tests. We excluded any individuals with physical abnormalities. Written informed consent was given by all participants after a full explanation of the study. The study was approved by the Review Board of Beijing Hui-Long-Guan Hospital.

Clinical Measurements

The Positive and Negative Syndrome Scale (PANSS) was used to assess each patient's psychopathology by two psychiatrists who had simultaneously received training in its use before the study started. After training, an inter-observer correlation coefficient >0.8 for the total PANSS score was maintained across repeated assessments.

Determination of Lipid Profiles

Blood samples were collected between 07:00 and 09:00 following an overnight fast. The biochemical analyses were performed by a technician who was blind to the clinical status of the participants. The serum levels of TC, TG, and HDL-c were determined by enzymatic methods (Beijing Leadman Biotechnology Co., Ltd, Beijing, China) using an Olympus AU2700 analyzer. The serum level of LDL-c was calculated using Friedewald's formula [20]. The serum level of total protein (TP) was determined using the bromocresol green method, and the serum level of albumin (Alb) was determined using the biuret method (Beijing Leadman Biotechnology). The serum level of globulin was calculated using the formula globulin = TP − Alb. The serum levels of apolipoprotein (Apo) A1 and ApoB were measured using the immunoturbidimetric method (Beijing Leadman Biotechnology) with the Olympus AU2700 analyzer.

Statistical Analysis

SPSS 15.0 (SPSS Inc, Chicago, USA) was used for statistical analysis. All data are expressed as mean ± SD. Since the clinical variables and the lipid profile variables were normally distributed in the smoker and non-smoker groups (Kolmogorov-Smirnov one-sample test), the principal analysis consisted of one-way analysis of variance (ANOVA). Because of group differences in age and duration of illness, analysis of covariance (ANCOVA) was also performed with these two covariates. The χ^2 test on categorical variables for demographic comparisons between the smoker and non-smoker groups was also administered. Pearson correlation coefficients were used to assess the correlations between biochemical markers and clinical ratings. Since both education and age were

negatively correlated with the number of cigarettes smoked in the smoker group, a partial correlation was also performed with education and age as covariates. In addition, since antipsychotic medications could alter the peripheral lipid profiles, medication was also treated as covariate in the partial correlation analysis.

Results and Discussion

Demographics

A demographic comparison between the two groups is shown in Table 1. Significant differences in age and duration of illness were found between the smokers and non-smokers. However, there were no significant differences between the two groups in education, age of onset, number of hospitalizations, body mass index (BMI), daily antipsychotic dose, and antipsychotic type. In addition, both age ($r = -0.282$, $P = 0.001$) and education ($r = -0.195$, $P = 0.047$) were negatively correlated with the number of cigarettes smoked per day in the smokers.

Symptoms and Lipid Profiles in Smokers Versus Non-smokers

The PANSS positive subscale was significantly lower in the smokers than in the non-smokers, but there were no significant differences in the PANSS total score or the negative and general psychopathology subscales (Table 2). The difference in the PANSS positive subscale remained significant after age and duration of illness were added as covariates. Furthermore, the number of cigarettes smoked per day was significantly associated with fewer negative subscales ($r = -0.265, P = 0.007$), even after age and education were adjusted as co-variables ($r = -0.192, P = 0.032$).

The levels of TP ($P < 0.05$) and globulin ($P < 0.005$) were lower in the smokers than in the non-smokers. When age and duration of illness were added as covariates, there was still a significant difference in globulin. Further, after co-varying for medication, this significant difference in globulin persisted. However, there were no significant differences in TC, TG, HDL-c, LDL-c, ApoA1, and ApoB between the smokers and the non-smokers. Finally, the positive PANSS subscale correlated with the serum level of HDL-c ($r = -0.309$, $P = 0.001$) in the smokers but not in the non-smokers. When medication was added as covariate, the correlation was still significant ($r = -0.297$, $P = 0.002$)

We found fewer positive symptoms in smokers than in non-smokers with schizophrenia, and the negative PANSS symptoms were lower in those who smoked more cigarettes. Unexpectedly, no significant differences were found in lipid profiles between the smokers and non-smokers. However, TP and globulin were significantly lower in the smokers than in the non-smokers, and the PANSS positive subscale correlated with the serum level of HDL-c in the smokers but not in the non-smokers.

The finding of fewer positive symptoms in schizophrenic smokers than non-smokers is consistent with previous studies which reported that cigarette smoking is associated with fewer negative symptoms in schizophrenia [4, 21–23]. A possible mechanism may be that chronic nicotine administration decreases the basal firing rates of dopamine neurons in the ventral tegmental area. Stimulation of nicotinic receptors enhances dopamine neuronal activity, but with desensitization of these receptors from chronic nicotine exposure, then dopamine activity would decrease. Dopamine catabolism in the dorsal striatum can also be increased by nicotine [24]. Reducing subcortical dopamine hyperactivity has been posited to reduce the symptoms of schizophrenia [25]. However, the exact

Table 1 Demographics of smokers and non-smokers with schizophrenia.

Variable	Smokers ($n = 104$)	Non-smokers ($n = 26$)	F or χ^2	df	P value
Age (years)	49.9 ± 7.5	56.7 ± 6.9	17.68	1,127	<0.001
Education (years)	9.4 ± 2.4	10.4 ± 3.0	3.12	1,128	0.079
Duration of illness (years)	25.9 ± 7.6	32.7 ± 9.6	15.01	1,127	<0.001
Age at onset (years)	24.1 ± 6.0	24.5 ± 5.9	0.074	1,128	0.786
Number of hospitalizations	4.0 ± 2.2	4.1 ± 2.3	0.116	1,128	0.734
BMI (kg/m^2)	23.9 ± 3.8	24.4 ± 3.6	0.284	1,128	0.595
Daily AP dose (mg) (CPZ equivalent)	419.5 ± 296.2	406.8 ± 612.7	0.022	1,128	0.884
Antipsychotic type: Typical/Atypical	47/56	13/16	0.006	1	>0.9

F, *F* statistic (ratio of mean squares used in ANOVA); df, degrees of freedom; AP, antipsychotic; CPZ, chlorpromazine; BMI, body mass index.

Table 2 Symptoms and lipid profiles in smokers and non-smokers.

Variables	Smokers (n = 104)	Non-smokers (n = 26)	F	df	P value
P subscales	14.5 ± 6.2	17.2 ± 4.8	4.316	1,128	0.040
N subscales	23.8 ± 6.2	24.7 ± 6.7	0.447	1,128	0.505
G subscales	33.7 ± 9.2	33.9 ± 7.6	0.019	1,128	0.891
PANSS total score	71.9 ± 17.6	75.8 ± 14.0	1.105	1,128	0.295
Triglycerides (mmol/L)	1.7 ± 1.0	1.7 ± 0.8	0.041	1,128	0.840
Total cholesterol (mmol/L)	4.3 ± 0.8	4.4 ± 0.8	0.532	1,128	0.467
HDL-c (mmol/L)	1.1 ± 0.2	1.1 ± 0.2	0.176	1,128	0.675
LDL-c (mmol/L)	2.8 ± 0.5	3.0 ± 0.6	0.902	1,128	0.344
ApoA1 (g/L)	1.2 ± 0.1	1.2 ± 0.2	0.033	1,128	0.855
ApoB (g/L)	0.7 ± 0.3	0.7 ± 0.1	0.211	1,128	0.647
Total protein (g/L)	65.1 ± 4.7	67.3 ± 4.4	4.752	1,128	0.031
Albumin (g/L)	41.1 ± 2.6	40.8 ± 2.1	0.336	1,128	0.563
Globulin (g/L)	24.0 ± 3.4	26.5 ± 4.4	10.338	1,128	0.002

F, F statistic (ratio of mean squares used in ANOVA); df, degrees of freedom; PANSS, Positive and Negative Syndrome Scale; P, positive symptom; N, negative symptom; G, general psychopathology; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Apo, apolipoprotein.

mechanism by which smoking improves the negative symptoms remains unknown.

Unexpectedly, we found no significant differences in the lipid profiles of smokers *versus* non-smokers. In the general population, smoking is associated with abnormal profiles, such as elevated TC, TG, LDL-c, and ApoB, and reduced HDL-c and ApoA1 [14–16], suggesting that smoking has potentially long-term atherogenic effects on lipid metabolism. The biological mechanisms linking smoking and atherogenesis are complex, but a presumed linkage is that nicotine stimulates the sympathetic adrenal system to secrete catecholamines [26] These catecholamines then increase lipolysis and the concentration of plasma free fatty acids, which in turn increases the synthesis of hepatic TG and VLDL-c in the blood stream [17, 18]. However, a possible explanation as to why we did not find similar increases in these measures is that the chronic, hospitalized male schizophrenic patients had been treated with antipsychotic medications for >25 years. Many previous studies have demonstrated that antipsychotic medications also alter peripheral and central nervous system lipid profiles [9–11, 27, 28]. These medications may have a greater influence than smoking on the same lipid profiles. The significant negative correlation between the positive PANSS subscales and the protective HDL-c serum levels may reflect an additive association between more symptoms and lower HDL-c levels among smokers. Since the non-smokers did not show any relationship between HDL-c levels and psychotic symptoms, they may be relatively protected from the effects of stress on these levels. Smoking may be a permissive risk factor that can extend beyond the strong antipsychotic medication effects that also decrease HDL-c levels. These results indicate that the effects of smoking on schizophrenia are not mediated through changes in the lipid profile, and that other pathways might be involved, e.g. the nicotine pathway, which should be investigated in more detail. Therefore, smoking may alter the lipid profile in a complex manner in the context of chronic antipsychotic treatment. Clearly, future studies should include outpatients early in their medication treatment, or first-episode or drug-naïve patients with schizophrenia, rather than our chronically hospitalized male patients who had more severe psychopathology and a longer illness duration than is typical of patients with schizophrenia.

We also found significant differences in the serum levels of TP and globulin between the smokers and non-smokers. The results were similar to a recent study which reported that current smoking is associated with changes of systemic immune and inflammation markers in older, long-term smokers [29]. It is well known that smoking has adverse effects on the immune system; the immunosuppressive properties of smoking have been well-established in both humans and experimental animal models [30, 31]. For example, smoking decreases the levels of anti-inflammatory cytokines such as interleukin (IL)-10 and augments the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor [32]. Thus, the results suggested that smoking is an important contributor to the altered immune system in patients with chronic schizophrenia [33]. In addition, various abnormalities in the immune system are associated with schizophrenia [34–37]. For example, two recent meta-analyses have shown cytokine alterations in schizophrenic patients. The first meta-analysis by Potvin *et al.* [38] found increased levels of peripheral IL-2R, IL-1RA, and IL-6 in schizophrenic patients. The second meta-analysis by Miller *et al.* [39] showed that the macrophage-derived cytokines

IL-1β, IL-6, and TNF-α, and the T helper 1-derived cytokines interferon-c and IL-12 are increased in first-episode psychosis. Moreover, immune activation is particularly prominent in schizophrenic patients resistant to therapy [40, 41]. Both antipsychotic medications and nicotine can decrease the activated immune response in patients with chronic schizophrenia [33, 41]. For example, we have reported that IL-2 and IL-6 are significantly lower in chronic schizophrenic smokers than in non-smokers, and lower IL-2 levels are correlated with smoking more cigarettes [33]. It is likely that the alterations of the immune system in schizophrenic smokers are caused by the combined effects of antipsychotic medications and smoking. However, it is noteworthy that the relationships between the serum levels of TP and globulin and these pro-inflammatory and anti-inflammatory cytokines are still unclear, and this deserves further investigation.

There were several limitations in this study. First, the participants were chronically hospitalized males with longer illness duration and more severe psychopathology than first-episode drug-naïve patients or typical outpatients with schizophrenia. Furthermore, the sample of non-smokers was small. Second, no healthy control group was included. Since the results for TG, TC, HDL, and LDL showed no differences between smokers and non-smokers in schizophrenic patients, it would be interesting to know if they differ from the "healthy" population. Third, some important variables related to lipid profiles, such as dietary habit, physical exercise, and presence of metabolic diseases and other major medical conditions and relevant treatments were not examined in this study, which may have biased the results.

In conclusion, schizophrenic patients who smoke appear to have fewer psychotic symptoms. The smoking effects on schizophrenia might not be mediated through changes in the lipid profiles and other pathways, such as the nicotine system, should be further investigated. On the other hand, smoking can be a health risk in schizophrenic patients. Perhaps a way to address these issues would be to develop specific nicotinic compounds for treating schizophrenia without causing adverse side-effects.

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