The association of change in serum cholesterol levels and clinical treatment response in patients with schizophrenia: a prospective, randomized and open-label study

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Abstract

Background: In the past, it was suggested that dyslipidemia was associated with clinical improvement in patients with schizophrenia treated with antipsychotics; however, measurement at a single time point post-treatment, as done in most studies, could have contributed to the inconsistent results. The aim of this study was to investigate whether changes in serum levels of lipid and other covariates were associated with clinical response in patients with schizophrenia treated with atypical antipsychotics, using repeated measurements and considering time effects. **Method:** A total of 90 patients with schizophrenia were enrolled in this 12-week prospective, randomized and open label study. Positive and Negative Syndrome Scale (PANSS) score and a standard serum lipid profile were measured at baseline (day 0) and subsequently followed up at weeks 4, 8 and 12. The generalized estimating equation (GEE) model was applied to examine the relationship between serum lipids and treatment response, controlling for other potential variables. **Results:** The results of GEE analysis showed that the increase in serum total cholesterol levels during 12 weeks' antipsychotic treatment was significantly associated with a reduction in PANSS total score ($\beta = -0.37$, $p = 0.02$) and positive symptom score ($\beta = -0.34$, $p = 0.01$) over time. **Conclusions:** These findings revealed that the change in serum total cholesterol level was positively associated with the therapeutic efficacy of atypical antipsychotics. Serum total cholesterol may be a potential predictor of clinical response in patients with schizophrenia treated with atypical antipsychotics. **Trial Registration:** ClinicalTrials.gov identifier: NCT03730857. The trial was retrospectively registered on 11 Feb, 2019.

Introduction

Schizophrenia is a severe mental illness causing considerable disability, and regular antipsychotic medication can help to alleviate the symptoms. Atypical antipsychotics have advantages over typical antipsychotics in schizophrenia treatment due to their low rate of adverse effects and potentially superior efficacy. However, there remain some issues to be addressed. Clinical use of antipsychotic drugs for the treatment of schizophrenia may be associated with weight gain, abnormal glucose metabolism, atherogenic lipid levels and increased risk of metabolic disorder [1–6]. A number of studies have reported that the therapeutic efficacy of antipsychotic medication is associated with weight change [7–12]. Nevertheless, weight change is a nonspecific physiological variable and changes in body weight alone are not sufficient to explain the potential mechanism of this relationship [13].

Previous studies have found that, compared with the healthy individuals, patients with schizophrenia have higher levels of serum lipids [5, 14–16]. Dyslipidemia has been demonstrated in untreated patients with schizophrenia [17,18]. These study findings revealed that lipid abnormalities are reflected by significant changes in the central nervous system as well as peripheral tissues, and serum lipoproteins may serve as a clue to the pathophysiology of schizophrenia. Several lines of evidence also suggest that dyslipidemia may be present in early stages of the disease, even before treatment is initiated [19,20]. Furthermore, dyslipidemia has been found in patients with first-episode psychosis (FEP) and in drug-naïve patients with schizophrenia [18,21,22]. These studies indicated that changes in lipid metabolism occur

during early development of the disease, which implies that the mechanism behind metabolic vulnerability may be related to the psychopathology of schizophrenia. We assumed that the changes in serum lipids, which may occur after an increase in body weight, can be used as a predictor for clinical improvement in patients treated with atypical antipsychotics.

It has been suggested that serum lipid concentration (total cholesterol and triglycerides) may be correlated with clinical effectiveness of clozapine [13,23,24]. The results show that an increase in either serum total cholesterol concentration or serum triglyceride concentration, or the combined effects of total cholesterol and triglycerides, are related to improvement in the clinical response of patients with schizophrenia receiving atypical antipsychotic medication. Lally et al. [23] reported that an increase in serum triglyceride level could predict clinical improvement in patients with schizophrenia taking clozapine. Interestingly, a recent study pointed out that the levels of triglycerides and cholesterol were negatively related to global functioning and that higher serum triglyceride levels were associated with more severe positive psychotic symptoms in schizophrenic patients treated with antipsychotics [25]. Further, a longitudinal study has reported that serum lipid levels are correlated with chronic symptom intensity in both acute and chronic stages of schizophrenia in patients receiving antipsychotics [16]. Recent meta-analyses found lower total cholesterol and LDL levels together with higher triglycerides in individuals with FEP [26–28]. This implies that dyslipidemia in patients with schizophrenia may not only result from the clinical use of antipsychotic medication but also be related to the illness itself.

Considering these inconsistencies, it is still uncertain whether lipid profiles are correlated with current symptom severity, and/or disease progression [29,30]. However, the inconsistencies may have resulted from the single post-treatment measurement used in most studies. The primary objective of this 12-week prospective, randomized and open label study was to investigate whether changes in serum lipid profiles were associated with clinical response in schizophrenic patients treated with atypical antipsychotics, using repeated measurements and considering time effects.

Methods

Study design

The study took place at Kaohsiung Armed Forces General Hospital in Kaohsiung, Taiwan. All study procedures were approved by the Institutional Review Board of Kaohsiung Armed Forces General Hospital, Taiwan (Protocol ID: T1–02). All participants provided written consent for all study procedures. This study was registered at clinicaltrials.gov (identifier NCT03730857) on Feb. 11, 2019, and followed CONSORT guidelines for a randomized trial (S1 Table).

Participants

Fig. 1 is a flowchart of the recruitment process. We recruited 101 eligible adult patients with schizophrenia who had had an acute psychotic episode and had been admitted to a psychiatric ward. We excluded 11 eligible patients because they refused to participate in the study. Ninety inpatients participated in this study and were randomly assigned to receive treatment with paliperidone ($n = 30$), risperidone ($n = 30$) or olanzapine ($n = 30$) in an allocation ratio of 1:1:1. Participants were assigned using simple randomization procedures (computerized random numbers) to one of the three treatment groups. The randomization was conducted by a research assistant who was blinded to each patient's status. This study complied with basic principles of balancing the likelihood of harm, the effectiveness of monitoring, and the potential severity of risk. The participants were required to be willing and able to be hospitalized, and the duration of hospitalization was at least 1 month before follow-up as outpatients.

The inclusion criteria for this study were: (1) age 18–65 years; (2) meeting the diagnostic criteria for schizophrenia according to the Diagnostic and Structural Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [31]; (3) not having received long-acting antipsychotic injections in the preceding 6 months; and (4) no major systemic illnesses based on physical examination and laboratory test results. The exclusion criteria were as follows: (1) history of clozapine treatment in the previous 6 months; (2) treatment with cholesterol or triglyceride-lowering medications; (3) substantial risks of suicide or violent behavior; (4) pregnancy or breastfeeding; (5) documented neurological or other medical disorder that could influence the function of the central nervous system; and (6) unstable or critical untreated medical illness.

Trial procedures

A triple therapy (paliperidone, risperidone and olanzapine) design was adopted in this study with a run-in period of 3 months. The patients were required to have discontinued all prior use of antipsychotics for at least 7 days before receiving one of the three atypical antipsychotics as a washout period.

The antipsychotic agents were administered with flexible dosing, which could be adjusted on the basis of the clinical judgment of the physicians in charge. The oral formulation was taken once daily and the recommended dosages for the three treatment groups were as follows: 6–12 mg paliperidone, 4–6 mg risperidone, and 10–20 mg olanzapine. Throughout the clinical trial, participants were permitted to use their concomitant medication continuously, including lorazepam (up to 6 mg/day) for sleep disturbance or agitation and biperiden (up to 6 mg/day) for treatment of extrapyramidal side effects. The use of other psychotropic agents and lipid-lowering medications was not allowed during the 3-month study.

Measurements

The initial evaluation included a comprehensive history comprising the patient's age at onset, duration of mental illness, educational level (years spent in school), family history of schizophrenia, and history of alcohol consumption and cigarette smoking. The clinical psychopathology of participants was assessed

by Positive and Negative Syndrome Scale (PANSS) ratings. The PANSS total score ranges from 30 to 210, with higher scores indicating more severe psychopathology. The PANSS includes 30 items measuring positive symptoms, negative symptoms and general psychopathology [32]. The raters who assessed the PANSS did not know the name of the assigned drug. The participants underwent evaluation of clinical psychopathology and metabolic parameters, including serum lipid levels and body mass index (BMI) at initial assessment (baseline, day 0) and were followed up at weeks 4, 8 and 12. In this study, we used the BMI to examine the individual variability in weight change. The height of each participant was measured at baseline, their weight was measured at each clinical visit, and the two measurements were used to calculate BMI (kg/m^2). Fasting morning blood samples for the laboratory investigation were initially drawn at baseline (after completion of drug washout), and then at weeks 4, 8 and 12. Analyses of serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride (TG) were carried out by the standardized, automated, high throughput enzymatic analyses, which achieved within- and between-run coefficients of variation of $< 5\%$ [33].

Statistical analysis

All numeric variables are presented as mean $\pm$ SD and categorical variables are summarized using frequencies and percentages. A series of repeated measures analyses of variance were then applied to evaluate continuous variables among the treatment groups. Post hoc analyses were conducted via Tukey tests.

We also applied generalized estimating equations (GEE) for repeated measures analysis and corrected within-subject correlations, and the statistical model was developed to establish a prognostic prediction model for the therapeutic effect of treatment of schizophrenia by atypical antipsychotics across all four time points (day 0 and weeks 4, 8 and 12) [34]. The therapeutic effect was determined by the mean change in PANSS scores. The GEE method is often used for marginal regression analysis of longitudinal data and other correlated response data, and is especially suitable for repeated measures studies. In addition to providing more efficient estimators of regression parameters, the main advantage of GEE is the comparison of correlated proportions using simulated data and coverage properties of the confidence interval. The GEE estimates average marginal effects and take into account the within-subject correlations by using an empirical covariance matrix.

We first used GEE linear regression models to evaluate adjusted associations between the lipid variables (total cholesterol, TG, HDL and LDL) and PANSS scores. The following baseline measures (see Table 1) were included as covariates in all adjusted analyses. We conducted a sequence of regression models adjusted for gender, age, age at onset, duration of mental illness (continuous), educational level (continuous), family history of schizophrenia (yes/no), history of alcohol consumption and cigarette smoking (yes/no), current type (categorical) and treatment dosage (continuous) of antipsychotics, and BMI (continuous). We then reduced this model by excluding covariates that did not predict the outcome with $p \leq 0.10$, or did not change the estimated association between lipid variables and PANSS score by $>$

10% when removed from the model. The result of the final model is shown in Tables 3 and 4. The time points (weeks) were entered as a within-subject factor in order to examine whether there was a significant time effect in the repeated measures analysis. The data analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA/IBM, New York, USA). Statistical significance was defined as $p < 0.05$ (two-sided).

Results

Ninety eligible patients (30 patients each in the paliperidone, risperidone and olanzapine groups) agreed to participate in this study initially. Twelve patients were lost from the study at week 8, and 14 at week 12. Out of the 90 participants, 76 completed the 3-month study period (84.4%). Failure to follow up was because the patients visited other hospitals (Fig. 1). No serious adverse effects were reported. Baseline demographic characteristics and clinical manifestations of the participants are presented in Tables 1 and 2. There were no significant differences in the demographic or baseline characteristics and mean PANSS total scores among the treatment groups.

The differences among the treatment groups in mean changes of PANSS total scores and lipid profiles over time are shown in Table 2 and Figure 2. All three groups showed a decrease in PANSS total score compared with baseline at weeks 4, 8 and 12. There were no significant differences in the levels of serum lipids among the three treatment groups at each time point.

In the GEE model, the PANSS total score and subscale scores (PANSS positive symptom score, negative symptom score and general psychopathological symptom score) were used as outcome variables while performing the appropriate statistical modeling to investigate the association of the lipid variables (collected over time) with the PANSS scores (also collected over time). The univariate and multivariate GEE analyses of the associations between the lipid variables and the PANSS scores, adjusted for baseline demographic and clinical data, are shown in Tables 3 and 4. The result of the GEE analysis showed that, within the participants tested, there was a significant time effect in the repeated measures analysis of PANSS ratings. We found that the increase in serum TC levels during 12 weeks of antipsychotic treatment was significantly associated with a reduction in PANSS total score ($\beta = -0.37$, $p = 0.02$) and positive symptom score ($\beta = -0.34$, $p = 0.01$) over time. This analysis revealed that there was no association between serum lipid changes and the PANSS negative symptom score or general psychopathology symptom score (data not shown). No other potential predictive factors were significantly associated with clinical treatment response. In terms of the relationship of serum lipid changes and psychopathology in schizophrenia, there was no significant difference among the three antipsychotic agents.

Discussion

The principal finding of this study was that, in patients with schizophrenia treated with atypical antipsychotics (olanzapine, risperidone or paliperidone), the increase in serum TC levels during 12 weeks of antipsychotic treatment was significantly associated with improvement in the clinical treatment

response (i.e. reductions in PANSS total score and positive symptom score). No other potential predictors, including clinical demographic data, current type and dosage of antipsychotics, or BMI and other lipid profiles, were associated with ultimate response in this study.

These results demonstrate that higher TC levels are associated with greater improvement in clinical treatment response over time in schizophrenic patients treated with atypical antipsychotics. This is consistent with the findings of many previous studies on second-generation antipsychotics, which indicate that an increase in TC is associated with subsequent improvement of symptom intensity and functioning [13,35–37]. In contrast with previous studies that only measured the lipid profiles once, we measured them repeatedly and used the GEE approach to investigate the association between changes in serum TC level and psychopathology throughout the follow-up period. With regard to the metabolic effects in patients with schizophrenia treated with antipsychotics, a previous meta-analysis has reported that the increase in TC may be due to time-dependent exposure [38]. Some longitudinal studies have shown that certain metabolic risk factors such as obesity and dyslipidemia may be present in the early stages of psychosis, prior to initiating treatment, and that the alteration in serum lipid profile is correlated with symptom intensity in schizophrenia [16,19,20]. The results of this study indicate that neither a reduction in PANSS general psychopathology nor a negative symptom score but a reduction in PANSS positive symptom score is associated with elevated serum total cholesterol levels.

Hyperlipidemia due to secondary causes is common and the etiology is important to recognize [39]. Currently, the most commonly used criterion for classifying overweight and obesity is BMI [40]. It has been found that the weight gain associated with antipsychotic treatment may be related to an improvement in psychosis in patients with schizophrenia [7–12]. Our findings suggest that an alteration in serum TC, independent of BMI, is associated with a change in symptom severity during antipsychotic treatment.

Hyperlipidemia refers to elevated levels of TC, TG and LDL, and reduced HDL concentration. Prior research has shown that there is a potential correlation between an increase in serum TG levels and clinical improvement during clozapine treatment [13,14,23]. However, we did not observe similar results in the patients treated with paliperidone, risperidone or olanzapine. A previous meta-analysis showed that the prevalence of low HDL cholesterol was significantly higher among medicated multi-episode patients with schizophrenia than in those with FEP and in antipsychotic-naïve patients [41]. There was also a report of an association between an increase in HDL level and improvement in psychotic symptoms in patients with FEP after 1 year of antipsychotic treatment [42]. The association between different lipid profiles, such as HDL, and changes of psychopathology in patients with schizophrenia may need further study. Moreover, a recent systematic review and meta-analysis of 20 case–control studies found significant reductions in TC and LDL cholesterol levels in patients with FEP, suggesting that hypercholesterolemia in patients with chronic schizophrenia seems to be secondary and potentially modifiable [28]. Several studies have shown that patients with schizophrenia develop alterations in lipids at the onset of illness, indicating that such alterations should be regarded as an intrinsic factor contributing to schizophrenia [43–45]. There is also some evidence supporting a potential relationship between altered serum

cholesterol level and psychiatric symptoms in patients with mental illness, as well as those with schizophrenia [46–48].

Many studies have been conducted to understand the mechanisms underlying the multifaceted role of lipids in psychosis; for example, changes in cell membrane lipid profiles have been linked to treatment response [17,49]. These findings indicate that genetic and molecular mechanisms could be involved in the association between serum lipid dysregulation and the risk of developing schizophrenia [50]. Three major types of lipid that are abundant in the brain membrane are phospholipids, cholesterol and glycerophospholipids [51–53]. An association between lipid profiles in serum and cell membranes and clinical symptoms in patients with schizophrenia has been demonstrated [25]. Accumulating evidence has also suggested a pivotal role for membrane-forming and signaling lipids of the brain in the pathogenesis of schizophrenia [54]. Furthermore, changes in the composition of membrane lipids in neuronal cells are correlated with neurotransmission, symptoms and behavior in schizophrenia [16]. Together, the associations between symptom severity and lipid levels suggest an important role of lipid biology in schizophrenia. Serum TC may be a potential biological predictor for treatment outcome in patients with schizophrenia undergoing drug therapy.

The strength of this study is that we conducted repeated measures of lipid levels (at time points 1–4) during the course of schizophrenia and studied their relationship with clinical symptom severity, which allowed us to investigate whether lipid profiles are associated with the pathogenesis of schizophrenia. This has not been done before in similar studies. However, the present study had some limitations that had to be taken into account before forming a conclusion. First, life-style factors, including daily dietary intake and exercise, are also recognized to influence lipid parameters, but these characteristics of the patients in this study were not controlled. Second, the small sample size in the groups given the different drugs may have increased the type I error rate. Third, identifying more substantial factors to correlate the therapy response with other factors (such as plasma levels of antipsychotic medication) in specific subgroups of patients may provide a rationale for this observation, and explain the drug response.

Conclusion

Serum TC, independent from BMI, may be used as one of the predictive indicators for treatment efficacy in patients with schizophrenia treated with paliperidone, risperidone or olanzapine. The findings of this study suggest that more research is warranted to determine the details of the underlying mechanisms and to elucidate the relationships between lipid biology and the pathophysiology of schizophrenia.

Supporting Information

S1 Table. CONSORT checklist. CONSORT 2010 checklist of information to include when reporting a randomized trial.

(DOCX)

Abbreviations

DSM-IV-TR: Diagnostic and Structural Manual of Mental Disorders, Fourth Edition, Text Revision

PANSS: the Positive and Negative Syndrome Scale

GEE: generalized estimating equation

BMI: body mass index

TC: total cholesterol

HDL: high-density lipoprotein cholesterol

LDL: low-density lipoprotein cholesterol

TG: triglyceride

FEP: first-episode psychosis

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kaohsiung Armed Forces General Hospital, Taiwan. All participants provided written consent.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YL contributed to the data collection and analyses, and writing of the manuscript. FW and MH supervised the execution and collection of data, participated in the development of the protocol, performed the final data analyses, and edited the manuscript. CC and KP contributed to the statistics advice, and made comments on and revised the manuscript.

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Tables

Table 1. Demographic and clinical characteristics of patients with schizophrenia treated with paliperidone, risperidone or olanzapine

	Paliperidone (<i>n</i> = 30)	Risperidone (<i>n</i> = 30)	Olanzapine (<i>n</i> = 30)	<i>p</i>
Sex, N(%)				0.92
Male	16 (53.3)	15 (53.5)	17 (56.7)	
Female	14 (46.7)	15 (46.4)	13 (43.3)	
Age, mean±SD (years)	36.21±11.27	35.04±9.85	35.60±11.26	0.78
Age at onset, mean±SD (years)	26.17±6.60	24.71±4.81	26.70±8.46	0.49
Duration of illness, mean±SD (years)	10.00±7.54	7.24±6.92	8.96±9.72	0.72
Educational level, mean±SD (years)	11.03±3.06	12.39±2.46	11.91±3.81	0.14
BMI, mean±SD (kg/m²)	24.58±4.64	24.69±4.15	25.01±5.03	0.45
Alcohol history, n (%)	5/25(16.7)	4/26(14.3)	6/24(17.0)	0.95
Smoking history, n (%)	15/15(50.0)	16/14(57.1)	14/16(43.4)	0.39
Family history of schizophrenia, n (%)	9/21(30.0)	7/23(25.0)	8/22(32.1)	0.70
TC, mean±SD (mg/dL)	145.77±83.61	139.39±87.59	153.57±85.41	0.055
TG, mean±SD (mg/dL)	169.53±79.09	167.61±70.84	175.65±87.01	0.11
HDL, mean±SD (mg/dL)	45.83±14.66	44.64±12.18	48.87±19.96	0.46
LDL, mean±SD (mg/dL)	112.10±37.44	104.25±28.16	119.26±41.03	0.22

Abbreviations: BMI: *body mass index*; HDL: *high-density lipoprotein*; LDL: *low-density lipoprotein*; TC: *total cholesterol*; TG; *triglyceride*.

Table 2. Change in mean PANSS total scores over time and comparative analysis among groups

Mean PANSS total scores	Group variable	n	Mean (SD)	SE	95% CI for mean		F	P
					Lower bound	Upper bound		
Mean PANSS total scores at baseline	Paliperidone	30	84.67(22.99)	4.20	76.08	93.25		
	Risperidone	30	94.39(23.40)	4.42	85.32	103.46		
	Olanzapine	30	89.85(22.29)	3.06	83.70	95.99		
	Total	90	89.59(22.83)	2.17	85.30	93.89	1.33	0.27
Mean PANSS total scores at Week 4	Paliperidone	30	74.19(19.01)	3.66	66.66	81.71		
	Risperidone	30	84.24(19.87)	3.98	76.04	92.44		
	Olanzapine	30	70.22(23.62)	3.88	62.34	78.09		
	Total	90	75.36(21.83)	2.31	70.76	79.96	3.30	0.04
Mean PANSS total scores at Week 8	Paliperidone	24	70.42(18.04)	3.68	62.80	78.03		
	Risperidone	25	82.60(18.20)	3.64	75.09	90.11		
	Olanzapine	29	68.94(24.43)	4.32	60.13	77.74		
	Total	78	73.59(21.47)	2.39	68.84	78.34	3.41	0.04
Mean PANSS total scores at Week 12	Paliperidone	23	72.17(19.90)	4.69	62.27	82.06		
	Risperidone	25	79.20(19.26)	3.85	71.25	87.15		
	Olanzapine	28	67.11(18.22)	3.44	60.04	74.17		
	Total	76	72.65(19.47)	2.31	68.04	77.26	2.68	0.08

CI: confidence interval; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation; SE: standard error. * $p < 0.05$ statistically significant.

Table 3. Generalized estimating equation results for association of serum lipid profiles with PANSS total score and change in PANSS total score over time

Independent variable	β	SE	95% CI	<i>p</i>
TG	-0.01	0.03	-0.05 to 0.07	0.69
TC	-0.03	0.02	-0.01 to 0.02	0.17
HDL	0.06	0.11	-0.25 to 0.18	0.77
LDL	-0.02	0.05	-0.12 to 0.08	0.67
Time (week)	-2.16	0.89	-3.90 to 0.42	0.11
TG×time	-0.03	0.03	-0.04 to 0.03	0.28
TC×time	-0.37	0.04	-0.44 to -0.18	0.02
HDL×time	0.07	0.12	-0.17 to 0.31	0.56
LDL×time	-0.09	0.07	-0.10 to 0.22	0.16

Dependent variable: PANSS total score.

Abbreviations: CI: confidence interval; β : regression coefficient; HDL: high-density lipoprotein; LDL: *low-density lipoprotein*; PANSS: *Positive and Negative Syndrome Scale*; SE: *standard error*; TC: *total cholesterol*; TG: *triglyceride*.

Table 4. Generalized estimating equation results for association of serum lipid profiles with PANSS positive symptom score and change in PANSS positive symptom score over time

Independent variable	β	SE	95% CI	<i>p</i>
Intercept	-0.02	0.01	-0.04 to 0.01	0.82
Age	-0.04	0.01	-0.02 to 0.01	0.19
HDL	0.05	0.04	-0.03 to 0.13	0.28
LDL	-0.04	0.24	-0.09 to 0.04	0.47
Time (weeks)	-0.20	0.74	-1.26 to 1.65	0.79
Intercept×time	0.13	0.03	-0.02 to 0.02	0.74
Age×time	-0.34	0.02	-0.43 to -0. 11	0.01
HDL×time	0.01	0.11	-0.02 to 0.02	0.36
LDL×time	-0.02	0.01	-0.05 to 0.01	0.87

Dependent variable: PANSS positive symptom score.

Abbreviations: CI: confidence interval; β : regression coefficient; HDL: high-density lipoprotein; LDL: *low-density lipoprotein*; PANSS: *Positive and Negative Syndrome Scale*; SE: *standard error*; TC: *total cholesterol*; TG: *triglyceride*.

Figures

Figure 1

Flow chart of participants through the study

Figure 2

Comparison of the mean lipid levels of patients with schizophrenia in the three groups

Supplementary Files

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- [S1Table.CONSORTchecklist.doc](#)