# Effects of phenothiazine drugs on serum levels of apolipoproteins and lipoproteins in schizophrenic subjects[1]

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**KEY WORDS** schizophrenia; phenothiazines; antipsychotic agents; lipoproteins; apolipoproteins

**ABSTRACT**

**AIM:** To investigate the risk factors and clinical significance of blood-lipid metabolic disorder in schizophrenic patients caused by phenothiazine treatment for long term (from 1 month to 25 years). **METHODS:** Serum levels of apolipoprotein AI (apoAI), apolipoprotein B (apoB), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC) were measured in 120 chronic schizophrenia patients, 50 vascular dementia, and 100 normal controls by the enzyme method and immune fluoroscopy turbidimetric method. **RESULTS:** The patients with schizophrenia and vascular dementia had significantly lower content of apoAI, HDL-C, and apoAI/apoB than those in normal control ($P<0.01$). Their apoB and TG levels were higher than the healthy control group ($P<0.01$). The TG contents in the negative group and the vascular dementia group were obviously higher than the positive group ($P<0.01$) while there was no marked difference between the TC levels in the three groups and the normal control group ($P>0.05$). **CONCLUSION:** The chronic schizophrenic patients have a blood-lipid metabolic disorder by long-term intake of phenothiazine drugs. It is suggested that the traditional treatment with antipsychotic should reformed, and that drugs of degrading lipid and coagulation should be used to prevent and reduce the risk factors causing the onset of cardiovascular and cerebrovascular diseases and delay the development of the disturbance of intelligence and dementia.

## INTRODUCTION

Antipsychotic agents are mainly used for prevention or treatment of schizophrenia and serious psychotic diseases. It is reported that 40 % of psychotic patients have poor response to traditional antipsychotic agents which cause high recrudescence rate. For a long term, there is no suitable monitor method of the selection of antipsychotic agents, forecast of curative effect, and adjustment of dose. So it has become an issue of international concern to study the curative effect and toxic and side effects, to improve the cognitive function and remote therapy for the prevention and treatment of mental diseases[1-4]. It has always been ignored by clinic that phenothiazines medicine cause serious obstacle and potential danger of blood lipid decompensation and gaining weight or fatty. This paper studies whether blood lipid increase can accelerate the formation of atherosclerosis and resistance to antipsychotics which will aggravate damage of cognitive function after the treatment with phenothiazines for schizophrenes, especially female, old, and organic patients. This study probes into the biological risk factors and the clinical significance of blood lipid meta-

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bolic disorder in schizophrenic patients taking phenothiazine drugs for long periods.

## SUBJECTS AND METHODS

**Patient group** One hundred and twenty inpatients in the Mental Department of People's Hospital of Wuhan University (60 males and 60 females, aging 18-59 a, with an average of 42 a) were divided into schizophrenia-positive group, according to CCMD-2-R diagnostic standard, by reference to Andersen Classification Standard. All patients had longly (1 month-25 years) taken phenothiazine drugs (chlorpromazine 300-600 mg daily, perphenazine 20-40 mg daily). Dynamic observation of blood lipid was taken before and after treatment of 10 first onsets.

**Demenia group** Fifty vascular demenia inpatients in accordance with CCMD-2-R diagnostic standards, whose aging range was from 48-74 years old, with an average of 58. They had longly taken phenothiazine drugs at the same dosage as above. The diet in the two groups contained 2200 calorie daily, including 67 % carbohydrate, 14 % protein, and 19 % fat. The patients took normal indoor and outdoor exercises, and 170 patients were normal in their liver kidney functions. The studied patients were all permitted by the local Independent Ethics Committee (IEC) Administration.

**Control group** One hundred healthy testers whose aging range was from 21 to 69 years old, with an average of 45. Clinical physical examination and laboratory examination showed normal result excluding mental, neural, cardiac, cerebral, hepatic, renal, and endocrine diseases. The three groups were examined in cubical venous blood after 12-14 h fasting.

**Determination method** CL-7200 type automatic biochemical analyzer was used, with the enzyme method and the immune fluoroscopy turbidimetric method, to determine the serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), apoprotein AI (apoAI), and apoprotein B (apoB) levels of serums.

**Statistical analysis** Data were expressed as the mean±SD and statistically analyzed with SPSS10.0 software.

## RESULTS

**Comparison between genders in the normal group** In the control group, females had a much higher HDL-C and apoAI level than males ($P<0.05$), while other items were quite similar ($P>0.05$, Tab 1, 2).

**Comparison between the patient group and the control group** The patient group had much lower blood HDL-C, apoAI, and apoAI/apoB than those in the control group ($P<0.01$), but they had much higher TG and apoB than those in the normal control group ($P<0.01$), TC levels in both groups were similar ($P>0.05$, Tab 1, 2).

**Tab 1. Comparison in blood lipid between patient and control group. Mean±SD. $^{b}P<0.05$ *vs* female control group. $^{f}P<0.01$ *vs* control group.**

| Group | *n* | TG/mmol·L$^{-1}$ | HDL-C/ mmol·L$^{-1}$ | TC/mmol·L$^{-1}$ |
|---|---|---|---|---|
| Control | | | | |
| Male | 50 | 1.27±0.23 | 1.29±0.24$^{b}$ | 4.6±0.4 |
| Female | 50 | 1.26±0.29 | 1.42±0.17 | 4.6±0.4 |
| Patients | | | | |
| Male | 60 | 2.7±0.8$^{f}$ | 1.1±0.4$^{f}$ | 4.7±0.7 |
| Female | 60 | 2.4±0.8$^{f}$ | 1.2±0.3$^{f}$ | 4.4±0.7 |

**Tab 2. Comparison in apolipoprotein between patient and control group. Mean±SD. $^{b}P<0.05$ *vs* female control group. $^{f}P<0.01$ *vs* control group.**

| Group | *n* | apoAI/g·L$^{-1}$ | apoB/g·L$^{-1}$ | apoAI/apoB |
|---|---|---|---|---|
| Control | | | | |
| Male | 50 | 1.32±0.17$^{b}$ | 0.83±0.19 | 1.59±0.18 |
| Female | 50 | 1.41±0.19 | 0.81±0.22 | 1.62±0.17 |
| Patient | | | | |
| Male | 60 | 1.1±0.4$^{f}$ | 0.9±0.3$^{f}$ | 1.2±0.4$^{f}$ |
| Female | 60 | 1.2±0.4$^{f}$ | 0.9±0.3$^{f}$ | 1.2±0.3$^{f}$ |

**Comparison between negative, positive groups with schizophrenia and vascular dementia group** The patients with negative symptoms were similar to the cerebrovascular dementia patients in the blood lipid change, especially in that the dementia patients TG and apoB levels were higher than those of the patients with positive symptoms. All the three groups had a drop in their HDL-C and apoAI levels, and the positive group had a lesser drop than the other two groups, but no statistical significance. There was no marked differ-

ence as to the TC levels among the groups ($P$>0.05, Tab 3, 4).

**Tab 3. Comparison in blood lipid between patient group and vascular dementia psychonosema group. Mean±SD. $^cP$<0.01 *vs* positive group.**

| Group | *n* | TG/mmol·L$^{-1}$ | HDL-C/ mmol·L$^{-1}$ | TC/mmol·L$^{-1}$ |
|---|---|---|---|---|
| Negative | 60 | 2.8±0.9$^c$ | 1.1±0.4 | 4.3±0.8 |
| Positive | 60 | 1.9±0.8 | 1.2±0.4 | 4.4±0.8 |
| Dementia | 50 | 2.9±0.9 | 1.1±0.5 | 5.1±0.9 |

**Tab 4. Comparison in apolipoprotein between patient and vascular dementia group. Mean±SD. $^cP$<0.01 *vs* positive group.**

| Group | *n* | apoAI/g·L$^{-1}$ | apoB/g·L$^{-1}$ | apoAI/apoB |
|---|---|---|---|---|
| Negative | 60 | 1.1±0.4 | 1.0±0.3$^c$ | 1.1±0.3 |
| Positive | 60 | 1.2±0.4 | 0.9±0.4 | 1.3±0.4 |
| Dementia | 50 | 1.1±0.4 | 1.0±0.3$^c$ | 1.1±0.4 |

**Dynamic observation of the blood lipid detection before and after treatment of 10 first onset inpatients** The 10 new inpatients had a blood TC (4.3±0.4) mmol/L, TG (1.25±0.29) mmol/L, HDL-C (1.38±0.21) mmol/L, apoAI (1.37±0.19) g/L, apoB (0.78±0.17) g/L, apoAI/apoB (1.6±0.22) before taking medicine. Treatment after five weeks, their TG raised to (1.88±0.4) mmol/L. At the sixth week, serum HDL-C and ApoAI reduced to (1.22±0.27) mmol/L and (1.19±0.25) g/L, respectively. The above indices had a statistic significance compared with pretreatment ($P$<0.05), while other indices had little changes ($P$>0.05).

## DISCUSSION

The persistent and core symptom of schizophrenia is the damage to the cognitive function, which in return affects the development of the mental symptoms, and is especially closely related with negative symptom. But its causes and effects have been unknown for a long time. Clinical data show that antipsychotics can increase the weight or cause obesity and worsen the damage of cognitive functions. Traditional antipsychotic (eg, phenothiazine) mainly functions by blocking $D_2$-receptor. It also acts on $D_1$-receptor, histamine $H_1$, 5-HT receptor, and acetylcholinergic receptor, *etc*. For instance, $D_2$-receptor blocking is related to kinetic slowness, while some acute cognitive function involvement is related to the sedation caused by $H_1$ receptor blocking. Chlorpromazine is even more obvious in this respect. The anticholinergic function in traditional antipsychotic can accelerate the damage to cognitive function especially the learning and immediate memory. Acetylcholinergic is a key neural medium. The septal area-hippocampus-marginal lobe cholingeric path is closely related to learning and memory (especially immediate memory). For example, the damage on the synaptic function of the cholingeric can result in intelligence damage.

Due to the diversification and easy selectivity of phenothiazine action on receptors, and the gap between the therapeutic dosage and toxic dosage is narrow. As the choice of medicine, therapeutic prediction and therapeutic dosage rely on experience, and the resultant therapeutic dosage becomes a hidden danger. Phenothiazine can cause serious lipid metabolic disorder to schizophrenic patients[1-3]. Literature abroad has reported: male schizophrenic patients taking phenothiazine drugs have a much reduced HDL-C level and a rise in TG level [4,5]. Our experiments showed that there was a marked difference in blood lipid and apoprotein between schizophrenic patients long taking phenothiazine drugs and the healthy people. The manifestation of lipid abnormality is that the protective factors such as apoAI and HDL-C levels which prevent atheriosclerosis (AS), resulting in the rise of the AS risk factor apoB and TG. In recent years, experts at home and abroad have all regarded the abnormal change of apoprotein level as a specific biological index for AS cardiovascular and cerebrovascular risks[6-8]. Because apoAI and apoB are respectively main proteins that constitute HDL and LDL. Molecular biological studies indicate that apoAI mainly activates lecithin cholesterol acyl transferring enzyme so that its alcohol esterifies the free cholesterol of the peripheral histiocyte and transfer it to the liver for further metabolism in order to prevent sedimentation of lipid and formation of AS, which helps the clearance of cholesterol in the cells. Therefore, apoAI and HDL-C are protective factors against AS. They are in negative correlation with the AS cardiovascular and cerebrovascular diseases. While apoB participates in the LDL initiation, recognition and promotes synthesizing of

chylomicrons into LDL, thus accelerating AS formation. The rise in apoB is in positive correlation with the risk of AS occurrence and development. The harmfulness of phenothiazine drugs causing high TG lies in that it can cause over formation of pathogenic and small and dense LDL in which there is little apoB lysyl-residue, and its power combining with the LDL receptor on the cell surfure is reduced so that it is difficult to remove from the circulation[9]. In addition, TG is weak in anti-oxidation and easy to be intaken by macrophage promoting the formation of foam cells and resulting in AS[10-12]. In recent years, people have become interested in various metabolic disorders accompanied by TG symptoms. High TG can cause the change in LDL granules and lower its affinity with LDL receptor. High TG is also accompanied by lower HDL-C. High TG can make the HDL granules smaller and speed up decomposition metabolism. Increase in Apoprotein AI clearance reduced the HDL granules in the blood. Therefore patients with low blood HDL-C were vulnerable to cardiovascular and cerebrovascular diseases because the ability of the lipoprotein containing rich TG to remove AS was weakened. On the other hand, high TG can promote thrombosis, a great deal of free fatty acid is produced and the VII factor is in a state excitation. Whereas the VII factor, plays an important role as "trigger" factor of the extrinsic coagulation system. High TG can result in endothelial damage which increases the activity of plasminogen activator inhibitor-1 (PAI-1) and decrease the synthesis of tissue-type plasminogen activator, (t-PA) and plasminogen, leading to the reduction of the total plasmin vitality. In these cases, the negative patients and the brain organic patients with psychonosema had similar blood lipid abnormality symptoms. The mental symptoms of the patients in the cerebral organic psychonosema group result from extensive brain tissue damage caused by cerebrovascular accident and AS. The pathogenic basis for the above change is AS, and the blood lipid disorder is an important risk factor of AS. Autopsy results had testified that cardiovascular and cerebrovascular diseases were closely related with AS. The blood lipid abnormality in cerebral infarction plays an important role in the pathogenic mechanism of intracranial and extracranial AS. Many clinical data showed that negative symptom patients had, to a certain degree, cerebral structural changes such as cerebral cortex atrophy and ventricular expansion. The blood lipid metabolic disorder caused by traditional antipsychotics will further impair the patients' cognitive function, which has an important prediction value for schizophrenia. Cognitive dysfunction is a core feature of the persistence of schizophrenia. Clinicians must pay special attention to this. To further prove the relation between the blood lipid and apoprotein metabolic disorder of schizophrenic patients and the phenothiazine, dynamic observation was also done to 10 initial inpatients on blood lipid and apoprotein before and after therapy. Before treatment, they were normal in TC, TG, HDL-C, apoAI, apoB, and apoAI/apoB. Treatment after six weeks, apoAI and HDL-C began to drop and TG rises. The difference has marked significance. Therefore, we believe that vasodilator drugs and degrading lipid and coagulation drugs should be taken in the course of treatment of schizophrenia to improve and protect cognitive function. Great care should be taken for senile dementia schizophrenia patients with hypertension and diabetes to reduce the risk factors that cause cardiovascular and cerebrovascular diseases for the improvement of curative effect of schizophrenia.

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