

ORIGINAL ARTICLE

Metformin treatment of antipsychotic-induced dyslipidemia: an analysis of two randomized, placebo-controlled trials

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Dyslipidemia is one of the most common adverse effects in schizophrenia patients treated with antipsychotics. However, there are no established effective treatments. In this study, data were pooled from two randomized, placebo-controlled trials, which were originally designed to examine the efficacy of metformin in treating antipsychotic-induced weight gain and other metabolic abnormalities. In total, 201 schizophrenia patients with dyslipidemia after being treated with an antipsychotic were assigned to take 1000 mg day⁻¹ metformin ($n = 103$) or placebo ($n = 98$) for 24 weeks, with evaluation at baseline, week 12 and week 24. The primary outcome was the low-density lipoprotein cholesterol (LDL-C) levels. After metformin treatment, the mean difference in the LDL-C value between metformin treatment and placebo was from 0.16 mmol l⁻¹ at baseline to -0.86 mmol l⁻¹ at the end of week 24, decreased by 1.02 mmol l⁻¹ ($P < 0.0001$); and 25.3% of patients in the metformin group had LDL-C ≥ 3.37 mmol l⁻¹, which is significantly $< 64.8\%$ in the placebo group ($P < 0.001$) at week 24. Compared with the placebo, metformin treatment also have a significant effect on reducing weight, body mass index, insulin, insulin resistance index, total cholesterol and triglyceride, and increasing high-density lipoprotein cholesterol. The treatment effects on weight and insulin resistance appeared at week 12 and further improved at week 24, but the effects on improving dyslipidemia only significantly occurred at the end of week 24. We found that metformin treatment was effective in improving antipsychotic-induced dyslipidemia and insulin resistance, and the effects improving antipsychotic-induced insulin resistance appeared earlier than the reducing dyslipidemia.

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INTRODUCTION

A large body of literature show that antipsychotics, particularly atypical antipsychotics cause serious adverse metabolic effects, which include dyslipidemia, weight gain, insulin resistance and glucose intolerance.^{1,2} According to a recent study in an Asia population, 66% of patients with chronic schizophrenia had dyslipidemia after treatment with an antipsychotic,³ although there is no difference between typical and atypical antipsychotics. Patients treated with clozapine and olanzapine are more likely to have weight gain,⁴ and elevated level of insulin and insulin resistance.⁵ Dyslipidemia is one of major factors leading to cardiovascular diseases, such as myocardial infarction and stroke.⁶ Patients with schizophrenia are twice as likely dying from cardiovascular disease as the general population, and tend to have an average of 9–12 years of life loss.^{7,8} The development of cardiovascular illness and early death in patients with schizophrenia are to a certain degree attributed to dyslipidemia.

Dyslipidemia is an imbalance of individual's lipid components, comprising elevated level of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, or reduced level of high-density lipoprotein cholesterol (HDL-C). It is generally believed that elevated LDL-C is directly associated with cardiovascular events, and is the primary target of lipid-lowering therapy.⁹ In China, Europe and the United States, guidelines for lower LDL-C levels are recommended; and aggressively lowering the level of LDL-C becomes particularly important.^{10–12}

Dyslipidemia has become a major concern in the treatment of psychosis. However, there is a relative lack of interventions to control antipsychotic-induced dyslipidemia.

Metformin, a biguanide, is a well-known for its use of treating type 2 diabetes mellitus.¹³ In our previous study, metformin can improve antipsychotic-induced weight gain and insulin resistance.^{14–16} Insulin resistance is recognized as an important metabolic defect linking the components of metabolic syndrome that includes atherogenic dyslipidemia,¹⁷ and induces systemic cardiovascular risk such as hypertension¹⁸ and hyperglycemia.¹⁹ The link between insulin resistance and dysregulation of lipoprotein metabolism is well established.^{20–22}

An animal study has found that metformin effectively ameliorate the development of risperidone-induced insulin resistance and dyslipidemia (that is, altered serum triglyceride and total cholesterol levels), which is mediated via improvement in insulin resistance.²³ In diabetic patients, metformin treatment appears to have some beneficial effects on circulating lipid levels by decreasing the concentrations of plasma triglycerides and LDL-C, increasing the level of HDL-C and ratio of HDL-C to LDL-C.²⁴ However, these effects depend on the improvement of insulin resistance. Therefore, it is reasonable to assume that metformin may attenuate antipsychotic-induced dyslipidemia through improving insulin resistance.

However, it remains unclear if metformin is effective in improving antipsychotic-induced dyslipidemia in patients who

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have weight gain and/or have developed insulin resistance after antipsychotic treatment. Whether or not the effect of metformin treatment on antipsychotic-induced dyslipidemia is attributed to the improvement of insulin resistance. Therefore, we designed this study to examine the effect of metformin treatment on antipsychotic-induced dyslipidemia and to determine the role of insulin resistance in metformin treatment-related changes in lipid profile in patients with schizophrenia.

MATERIALS AND METHODS

Study design and data

The study was designed using two independent double-blind, randomized, placebo-controlled 6-month clinical trials of metformin in antipsychotic-induced dyslipidemia, weight gain and other metabolic changes. Although the first trial (STUDY 1, NCT01778244; recruitment, 2008–2012) was to examine the efficacy of metformin for treatment of antipsychotic-induced dyslipidemia; the second trial (STUDY 2, NCT01206153) was initially designed to investigate the efficacy of metformin in the treatment of antipsychotic-induced amenorrhea and weight gain. The data from the STUDY 1 have not been published elsewhere, although the primary outcomes of the STUDY 2 have been published.¹⁴

Two studies were identical in terms of measurements on lipids, weight gain and other serum chemicals. In STUDY 1, patients had to have an antipsychotic-induced dyslipidemia to meet the eligibility for the study; whereas in STUDY 2, all patients were women with antipsychotic-induced amenorrhea. Both studies were conducted in the Mental Health Institute of the Second Xiangya Hospital at the Central South University, China and two data sets were combined after that initial examination found little difference in related demographics and metabolic outcome measurements at baseline. Total 162 patients from STUDY 1 and 39 patients (all females) from STUDY 2, after excluding 45 patients who did not have dyslipidemia at the beginning of STUDY 2, were included for this analysis.

Participants

Patients aged 18–40 years with a first psychotic episode of schizophrenia diagnosed in accordance with criteria set out in the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV) were eligible for our study,²⁵ and the Structured Clinical Interview of DSM-IV Axis I Disorders (SCID-1), Clinical Version, was used during the screening phase.²⁶ To be qualified for the STUDY 1, patients had to meet: (1) have experienced dyslipidemia as defined below within the first year of treatment with one of four antipsychotics—clozapine, olanzapine, risperidone or sulpiride; (2) had been either discharged from inpatient units or first visit in the outpatient clinic in the 12 months before enrollment, and their lipid level, weight and antipsychotic treatment were documented; (3) had taken single antipsychotic medication, with no more than a 25% change in dosage, over the past 3 months. Dyslipidemia was defined on the basis of the Chinese guidelines for dyslipidemia in clinical practice using total cholesterol, triglyceride, HDL-C and LDL-C to guide treatment. It was defined as normal (no dyslipidemia) if total cholesterol $< 5.18 \text{ mmol l}^{-1}$ (200 mg dl^{-1}), triglyceride $< 1.70 \text{ mmol l}^{-1}$ (150 mg dl^{-1}), HDL-C $\geq 1.04 \text{ mmol l}^{-1}$ (40 mg dl^{-1}) and LDL-C $< 3.37 \text{ mmol l}^{-1}$ (130 mg dl^{-1});¹⁰ otherwise as dyslipidemia if patients had exceeded the threshold in either of four lipid measures. All participants had to be under the care of a parent or another adult caregiver who monitored and recorded the intake of medication daily during the trial to assure the adherence to medication. Patients were excluded from the study if there was evidence of liver or renal dysfunction, cardiovascular disease or diabetes mellitus; or if they were pregnant or lactating; or had any psychiatric diagnosis other than schizophrenia. For the STUDY 2, the inclusion and exclusion criteria have been previously described,¹⁴ and it followed the similar protocol as in the STUDY 1. All participants were followed for 24 weeks after starting metformin treatment.

Pharmacological intervention

Participants were randomly assigned to receive metformin (1000 mg day^{-1}) or placebo for up to 6 months. The dosage of 1000 mg day^{-1} metformin was based on safety and efficacy for Chinese diabetic patients with dyslipidemia.²⁷ For the first 3 days, participants took 250 mg of metformin or placebo twice a day, one before lunch and one before dinner. From day

4 onward, they took 500 mg of metformin or placebo twice a day. Any antipsychotics that patients were taking before enrollment in the study remained at the same dosage throughout the course of the study. Only trihexyphenidyl for extrapyramidal symptoms and lorazepam for insomnia or agitation were considered concomitant medications and were allowed as needed during the study period. Patients' adherence to the study medication for each visit was defined as having taken $> 80\%$ of the study drug dose prescribed for that period. If a participant was not adherent, both patient and caregiver were counseled on the importance of taking the prescribed medications of study.

Primary and secondary outcome measurements

The primary outcome was the level of LDL-C or the percentage of patients who had LDL-C $\geq 3.37 \text{ mmol l}^{-1}$ (130 mg dl^{-1}). The secondary outcomes were fasting triglyceride, total cholesterol, HDL-C, insulin and glucose levels, insulin resistance index, body weight, body mass index and Positive and Negative Syndrome Scale (PANSS) score, as well as incidence of adverse events. Body mass index was calculated as weight in kilograms divided by height in meters squared. Insulin resistance index was calculated based on the homeostasis model assessment²⁸ as: fasting insulin (mIU l^{-1}) \times fasting glucose (mmol l^{-1})/22.5.

The baseline data included related demographics, a comprehensive medical history, clinical evaluations of psychiatric symptoms, a physical examination with measurements of weight and height, and related laboratory tests. The PANSS²⁹ and the Treatment Emergent Symptom Scale³⁰ were used for monitoring psychiatric symptoms and adverse effects. Research nurses who performed all assessments were blind to the type of treatments. The baseline laboratory tests included level of fasting LDL-C, triglyceride, cholesterol, HDL-C, glucose and insulin, lactic acid in serum, liver and renal function tests, blood counts and electrocardiogram. Fasting blood samples were drawn after confirmation with patients or their caregivers.

Follow-up visits were made at weeks 12 and 24 after starting treatment. At each follow-up visit, all baseline evaluations including physical examination, laboratory tests, weight and height measurements, and Treatment Emergent Symptom Scale were repeated. The PANSS was administered again at week 24. Lipid levels, glucose and lactic acid levels, liver and renal function tests were determined by enzymatic procedures of the Boehringer Mannheim/Hitachi 714 automated chemistry analyzer (Hitachi, Tokyo, Japan). Serum insulin level was measured with a solid-phase radioimmunoassay. Weight and height measurements were made after participants removed their shoes and upper garments, and donned an examination gown.

Statistical analysis

Single variate descriptive analysis was performed to examine the difference in demographics and metabolic measures at baseline between two trials and two treatment groups in the combined data. Necessary statistical tests were performed, in which χ^2 test was for categorical variables; and *t*-test and general linear model while adjusting for related covariates were used to test for continuous variables at the baseline. Analysis of within-group time effect and modeling the treatment effect by time while controlling for age, sex and duration of illness was performed using general linear mixed model, which is an effective way to analyze quantitative outcomes before and after treatment in clinical trial;^{31,32} and *post-hoc* least square estimates of mean were obtained based on modeling results. The difference was considered statistically significant if a two-tailed *P*-value was < 0.05 . Analysis was performed using SAS 9.13 (SAS Inc., Carry, NC, USA).

RESULTS

Demographics and baseline outcome measurements

The demographics and outcome measurements at baseline were comparable between two trials (Table 1). Among 162 patients (81 females and 81 males) in STUDY 1 and 39 patients (39 females) in the STUDY 2, no significant difference in the mean of age (26.13 vs 25.54 years), and the duration of illness (8.64 vs 9.28 months) were found between STUDY 1 and STUDY 2. Although not observing any significant difference in body mass index, fasting glucose, insulin, insulin resistance index, HDL-C, LDL-C ($P > 0.05$) at baseline, a significant difference in total cholesterol (5.22 vs 4.81 mmol l^{-1} , $P < 0.0001$) and triglyceride (2.40 vs 1.79 mmol l^{-1} ,

Table 1. Summary of demographics and metabolic measures by study

	STUDY 1 (n = 162)			STUDY 2 (n = 39)			P-value
	Median	Mean	s.d.	Median	Mean	s.d.	
Age	25.00	26.13	4.66	25.00	25.54	4.37	0.2275
Duration of illness ^a	8.50	8.64	2.58	10.00	9.28	2.67	0.0936
Body weight (kg)	65.00	65.33	6.05	65.00	64.49	4.69	0.1847
Body mass index (kg m ⁻²)	24.45	24.72	1.26	24.45	24.59	1.21	0.9346
Fasting glucose (mmol l ⁻¹)	5.23	5.29	0.42	5.22	5.31	0.38	0.9924
Insulin (mIU l ⁻¹)	25.37	27.07	7.87	21.03	24.89	7.95	0.6826
Insulin resistance index	5.80	6.41	2.19	4.88	5.97	2.33	0.4206
HDL-C (mmol l ⁻¹)	0.98	0.92	0.28	1.07	1.01	0.24	0.0535
LDL-C (mmol l ⁻¹)	3.12	3.60	1.50	3.45	3.55	1.41	0.3272
Total cholesterol (mmol l ⁻¹)	5.04	5.22	1.58	4.84	4.81	1.47	< 0.0001
Triglyceride (mmol l ⁻¹)	2.03	2.40	1.04	1.69	1.79	0.93	0.0286
PANSS	48.00	47.27	8.13	48.00	47.46	6.74	0.9018

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PANSS, positive and negative syndrome scale score.
^aDefined from the first symptom to the time of participation in the study.

Table 2. Dyslipidemia defined by each single outcome measurement at baseline in metformin and placebo group

	Metformin		Placebo		Chi-Sq	P-value
	N	%	N	%		
STUDY 1	78		84			
Total cholesterol (≥5.18 mmol l ⁻¹)	51	65.4	25	29.8	20.61	< 0.0001
Triglyceride (≥1.70 mmol l ⁻¹)	73	93.6	61	72.6	12.44	0.0004
HDL-C (< 1.04 mmol l ⁻¹)	52	66.7	53	63.1	0.23	0.6343
LDL-C (≥3.37 mmol l ⁻¹)	38	48.7	39	46.4	0.09	0.7706
STUDY 2	25		14			
Total cholesterol (≥5.18 mmol l ⁻¹)	6	24.0	8	57.1	4.28	0.0385
Triglyceride (≥1.70 mmol l ⁻¹)	10	40.0	9	64.3	2.12	0.1455
HDL-C (< 1.04 mmol l ⁻¹)	7	28.0	8	57.1	3.22	0.0727
LDL-C (≥3.37 mmol l ⁻¹)	15	60.0	7	50.0	0.37	0.5458
STUDY 1 + STUDY 2	103		98			
Total cholesterol (≥5.18 mmol l ⁻¹)	57	55.3	33	33.7	9.53	0.0020
Triglyceride (≥1.70 mmol l ⁻¹)	83	80.6	70	71.4	2.32	0.1281
HDL-C (< 1.04 mmol l ⁻¹)	59	57.3	61	62.2	0.51	0.4733
LDL-C (≥3.37 mmol l ⁻¹)	53	51.5	46	46.9	0.41	0.5219

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

$P=0.0286$) was noted between STUDY 1 and STUDY 2. Therefore, study was coded as a binary variable, which was then used as a control variable in the combined data analysis, in particular for these two outcomes that showed difference between treatment and placebo group.

The demographics and outcome measurements at baseline between metformin and placebo group were examined in each individual study and in the combined data. The distribution of antipsychotics used in patients with schizophrenia were 47.8% for olanzapine, 27.4% for risperidone, 14.3% for clozapine and 10.4% for sulpiride; and there were no significant difference between metformin treatment and placebo group ($P=0.5104$) (Supplementary Table S1). In STUDY 1, a difference in total cholesterol between metformin treatment (mean = 5.69 mmol l⁻¹) and placebo group (mean = 4.78 mmol l⁻¹) was founded ($P < 0.0001$); whereas in STUDY 2, a differences in body weight ($P=0.016$), HDL-C ($P=0.030$) and triglyceride ($P=0.043$) between metformin treatment and placebo group were noted (Supplementary Table S2). When two data sets from STUDY 1 and STUDY 2 were combined, only a difference in total cholesterol remained, and it became smaller. The mean of total

cholesterol was 5.41 mmol l⁻¹ in metformin group, greater than the cutoff defining for dyslipidemia (5.18 mmol l⁻¹), and also higher than the mean of 4.86 mmol l⁻¹ in placebo group.

The percentage of dyslipidemia defined by four outcome measurements were different between metformin and placebo, and between two trials. However, the differences were diminished in the combined data set (Table 2). In STUDY 1, the percentage of dyslipidemia defined by all four measurements were higher in the metformin group than the placebo group; and they were significantly different in that defined by total cholesterol (65.4% vs 29.8%, $P=8.44 \times 10^{-06}$) and triglyceride (93.6% vs 72.6%, $P=3.76 \times 10^{-04}$). Although in STUDY 2, the percentage of dyslipidemia defined by total cholesterol, triglyceride and HDL-C were higher in placebo than metformin group. However, they were not statistically significant except total cholesterol, likely due to a smaller sample size. When two data sets were combined, the percentage of dyslipidemia was only significant in that defined by total cholesterol between metformin and placebo group (55.3% vs 33.7%, $P=0.002$). This was consistent with the difference in the mean of total cholesterol between metformin and placebo group.

Table 3. Descriptive statistics of outcome measures between metformin and placebo group at baseline, week 12 and week 24 in combined STUDY 1 and STUDY 2

	Baseline			Week 12			Week 24			P-value	Sig
	N	Mean	s.d.	N	Mean	s.d.	N	Mean	s.d.		
<i>Body weight (kg)</i>											
Metformin	103	64.78	6.10	102	64.21	6.45	99	63.56	7.65	0.0164	*
Placebo	98	65.57	5.50	95	65.78	5.19	91	65.71	5.18	0.0028	**
<i>Body mass index (kg m⁻²)</i>											
Metformin	103	24.57	1.29	102	24.39	1.61	99	24.12	2.21	0.0504	
Placebo	98	24.83	1.19	95	24.94	1.19	91	24.95	1.15	0.0015	**
<i>Fasting glucose (mmol l⁻¹)</i>											
Metformin	103	5.32	0.42	102	5.39	0.46	99	5.41	0.40	0.3119	
Placebo	98	5.27	0.41	95	5.34	0.40	91	5.25	0.39	0.1802	
<i>Insulin (mIU l⁻¹)</i>											
Metformin	103	26.15	8.09	102	24.24	6.78	99	22.72	6.79	< 0.0001	**
Placebo	98	27.17	7.72	95	29.56	9.15	91	29.56	8.04	0.0218	*
<i>Insulin resistance index</i>											
Metformin	103	6.31	2.45	102	5.80	1.66	99	5.45	1.62	< 0.0001	**
Placebo	98	6.40	2.05	95	7.04	2.32	91	6.92	2.02	0.0203	*
<i>HDL-C (mmol l⁻¹)</i>											
Metformin	103	0.97	0.26	102	0.98	0.22	99	0.99	0.20	0.5367	
Placebo	98	0.90	0.29	95	0.85	0.33	91	0.83	0.28	0.1041	
<i>LDL-C (mmol l⁻¹)</i>											
Metformin	103	3.69	1.52	102	3.48	1.24	99	3.02	0.81	< 0.0001	**
Placebo	98	3.50	1.43	95	3.65	1.38	91	3.89	1.24	0.0185	*
<i>Total cholesterol (mmol l⁻¹)</i>											
Metformin	103	5.41	1.57	102	5.10	1.19	99	4.86	0.99	< 0.0001	**
Placebo	98	4.86	1.51	95	4.92	1.68	91	5.51	1.57	0.0004	**
<i>Triglyceride (mmol l⁻¹)</i>											
Metformin	103	2.31	1.02	102	2.25	0.83	99	2.10	0.79	0.1238	
Placebo	98	2.25	1.08	95	2.37	0.95	91	2.51	1.09	0.2149	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. P*, P-value was for testing for the effect of treatment and placebo over time by group while adjusting for age, duration of illness, and type of medication using general linear mixed model, *P < 0.05, **P < 0.01.

Within-group trend and treatment effect

Table 3 presents the mean of all outcome measurements over the time period of treatment between metformin and placebo group in the combined data of STUDY 1 and STUDY 2. In total, there were 201 patients, 103 of them treated with metformin and 98 with placebo. During the course of treatment, all patients had a good medication adherence. Only 1 of 103 patients in the metformin group, and 3 of 98 patients in the placebo group discontinued before week 12 because of loss to follow-up, and 7 patients (3 metformin and 4 placebo) discontinued before week 24 because of loss to follow-up. Patients and their caregivers reported that 86–100% of patients in both groups had >80% of their medications.

Descriptive analysis showed that two treatment groups tend to have different trends within group. Schizophrenia patients treated with metformin showed a decreased trend in the level of insulin and lipids over time. After medication, the level of insulin was reduced from 26.15 mIU l⁻¹ at baseline to 22.72 mIU l⁻¹ at week 24 (P < 0.0001), insulin resistance index from 6.31 to 5.45 (P < 0.0001), LDL-C from 3.69 to 3.02 mmol l⁻¹ (P < 0.0001) and total cholesterol from 5.41 to 4.86 mmol l⁻¹ (P < 0.0001). In contrast, schizophrenia patients treated with placebo appears to have an increased body weight (P = 0.0028), body mass index (P = 0.0015) and total cholesterol (P = 0.0004).

Compared with the placebo, metformin treatment have a significant effect on the level of insulin after adjusting for sex, age, duration of illness, type of medication and study cohort. Analysis of data using general linear mixed model with treatment and time interaction showed that metformin treatment effects on insulin level changed significantly over time (Table 4). Schizophrenia patients treated with metformin tend to reduce body weight, body mass index, insulin and insulin resistance index. At baseline, there is no difference in all these outcome measurements between metformin and placebo group. Metformin treatment had significant effect on the mean difference in body weight from -0.60 kg at baseline to -2.1 kg at week 24 (P = 0.0007), body mass index from -0.33 to -0.89 kg m⁻² (P = 0.0016), insulin from -1.59 to -7.51 mIU l⁻¹ (P < 0.0001) and insulin resistance index from -0.23 to -1.64 (P < 0.0001). It is interesting to note that these effects appear at week 12, and further continued at week 24. However, we did not observe any significant effect of metformin treatment on fasting glucose (P = 0.3253).

We found that metformin treatment had significant effects on reducing dyslipidemia. After treatment, the mean difference in LDL-C between treatment and placebo group changed from 0.16 mmol l⁻¹ at baseline to -0.86 mmol l⁻¹ at the end of week 24, an decrease by 1.02 mmol l⁻¹ because of the metformin treatment (P < 0.0001); the mean difference in total cholesterol was from

Table 4. Estimates of treatment effect of metformin on weight gain, insulin and outcome measures in STUDY 1 and STUDY 2 from general linear mixed model while controlling for age, duration of illness, gender and type of medication

Time	Estimate	s.e.	DF	t	Pr > t	P-value
Body weight (kg)						
Baseline	-0.6027	0.704	233	-0.86	0.3928	0.0007
Week 12	-1.5674	0.7061	235	-2.22	0.0274	
Week 24	-2.0836	0.7084	238	-2.94	0.0036	
Body mass index (kg m⁻²)						
Baseline	-0.3286	0.2149	270	-1.53	0.1274	0.0016
Week 12	-0.6579	0.2159	274	-3.05	0.0025	
Week 24	-0.8919	0.217	279	-4.11	<0.0001	
Fasting glucose (mmol l⁻¹)						
Baseline	0.047	0.0599	564	0.78	0.4332	0.3253
Week 12	0.0452	0.0605	564	0.75	0.4554	
Week 24	0.1536	0.0614	565	2.5	0.0126	
Insulin (mIU l⁻¹)						
Baseline	-1.5858	1.1202	385	-1.42	0.1577	<0.0001
Week 12	-5.9613	1.1294	390	-5.28	<0.0001	
Week 24	-7.5097	1.1404	398	-6.59	<0.0001	
Insulin resistance index						
Baseline	-0.2283	0.2955	390	-0.77	0.4401	<0.0001
Week 12	-1.405	0.2979	395	-4.72	<0.0001	
Week 24	-1.6424	0.3009	403	-5.46	<0.0001	
HDL-C (mmol l⁻¹)						
Baseline	0.0492	0.0387	339	1.27	0.2041	0.0364
Week 12	0.1114	0.039	345	2.86	0.0045	
Week 24	0.1405	0.0393	352	3.58	0.0004	
LDL-C (mmol l⁻¹)						
Baseline	0.1633	0.1786	312	0.91	0.3611	<0.0001
Week 12	-0.1869	0.1797	317	-1.04	0.2991	
Week 24	-0.8646	0.181	323	-4.78	<0.0001	
Total cholesterol (mmol l⁻¹)						
Baseline	0.7005	0.1991	370	3.52	0.0005	<0.0001
Week 12	0.3588	0.2007	375	1.79	0.0746	
Week 24	-0.4914	0.2026	383	-2.43	0.0157	
Triglyceride (mmol l⁻¹)						
Baseline	0.1097	0.1388	474	0.79	0.4299	0.0158
Week 12	-0.08	0.1401	478	-0.57	0.5684	
Week 24	-0.3656	0.1418	484	-2.58	0.0102	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

0.70 to -0.49 mmol l⁻¹, decreased by 1.19 mmol l⁻¹ ($P < 0.0001$); and 0.11 to -0.37 mmol l⁻¹ in triglyceride, decreased by 0.48 mmol l⁻¹ ($P = 0.0158$). In contrast, the mean difference in HDL-C increased from 0.05 mmol l⁻¹ at baseline to 0.14 mmol l⁻¹ at week 24 ($P = 0.0364$). It is interesting to note that except HDL-C, all these treatment effects on lipid level did not appear until the end of week 24.

In term of dyslipidemia measured by LDL-C as a binary outcome, the overall treatment effect was still significant among 190 patients (99 metformin and 91 placebo) who completed the trials. At the end of trials, only 25.3% (25/99) of patients in the metformin group had dyslipidemia defined by LDL-C (≥ 3.37 mmol l⁻¹ or 130 mg dl⁻¹), compared with 64.8% (59/91) in the placebo group ($\chi^2 = 30.12$, $df = 1$, $P < 0.001$). For those who had dyslipidemia by LDL-C level at baseline, 64.0% (32/50) of patients who took metformin restored their LDL-C to below the

normal level, compared with 23.3% (10/43) who took placebo ($\chi^2 = 15.49$, $df = 1$, $P < 0.001$). In contrast, in the placebo group, for those patients who had a normal LDL-C at baseline, 54.2% of them (26/48) had an increase in their LDL-C level to ≥ 3.37 mmol l⁻¹ (130 mg dl⁻¹), compared with 14.3% (7/49) taking metformin ($\chi^2 = 17.18$, $df = 1$, $P < 0.001$). We did not perform multiple regression analysis of the binary outcome because of limited sample size.

Insulin resistance on metformin treatment effect

Suspecting that the effect of metformin treatment on dyslipidemia may act through the improvement of insulin resistance, we examined further treatment effect on dyslipidemia while controlling for the level of insulin resistance, measured by insulin resistance index. At baseline, correlation analysis of outcome measurements showed that body weight, body mass index, fasting glucose, insulin and insulin resistance index were moderately correlated and clustered together ($r > 0.30$). LDL-C and total cholesterol were correlated, but HDL-C and triglyceride appear independent of all other outcome measurements (Supplementary Table S4).

Insulin resistance appears to have little impact on the improvement of dyslipidemia after metformin treatment (Table 5). When insulin resistance index was included as a covariate in the multiple regression analysis, the effect of metformin treatment on HDL-C became nonsignificant ($P = 0.1325$). In contrast, after controlling for insulin resistance index, metformin treatment still have significant effect on LDL-C ($P < 0.0001$), total cholesterol ($P < 0.0001$) and triglyceride ($P = 0.0191$). When the analysis was stratified by sex, we found that metformin treatment had significant effect on LDL-C ($P < 0.0001$), total cholesterol ($P = 0.0001$) and triglycerides ($P = 0.0027$) in men; only significant effects on LDL-C ($P < 0.0001$) and total cholesterol ($P = 0.0014$) were observed in women, which are largely consistent between men and women. *Post-hoc* analysis showed that the metformin treatment effects only occurred significantly at week 24. These suggest that metformin treatment on the improvement of LDL-C, total cholesterol and triglyceride is independent from insulin resistance.

Adverse events

There were no significant differences in the frequency and types of adverse events reported between the two groups. Adverse events that affected >5% of the overall sample were showed at Supplementary Table S5. No hypoglycemia was reported during the trial. Serum lactic acid levels, liver and renal function tests, and electrocardiogram results remained normal in all patients throughout the course of the treatment, and there were no episodes of vomiting or lactic acidosis.

DISCUSSION

To our knowledge, this is the first clinical trial that examines the effect of metformin treatment on antipsychotic-induced dyslipidemia in patients with first-episode schizophrenia. After a 24-week trial, we found that metformin treatment had significant effect on not only controlling weight gain, insulin and insulin resistance, which is consistent with our previous studies,^{5,14-16} but also significantly improving the altered level of lipids, including LDL-C, HDL-C, total cholesterol and triglycerides in blood. These effects on insulin and lipids were in a time-sequence manner, and improvement of lipid profile was at least partly independent of reducing insulin resistance.

Our findings that metformin treatment decrease antipsychotic-induced elevation of LDL-C levels are consistent with previous studies in patients with diabetes^{24,33} and schizophrenia patients,³⁴ as well as an animal study that showed treatment effect on triglyceride and total cholesterol.²³ In study of schizophrenia

Table 5. Metformin treatment effect on dyslipidemia after controlling for level of insulin resistance index in the combined data

Time	All (n = 201)			P-value	Male (n = 81)			P-value	Female (n = 120)			P-value
	Estimate	t	Pr > t		Estimate	t	Pr > t		Estimate	t	Pr > t	
HDL-C												
Baseline	0.0463	1.20	0.2320	0.1325	0.0418	0.85	0.3984	0.3789	0.0515	0.82	0.4107	0.2389
Week 12	0.0932	2.35	0.0191		0.0707	1.40	0.1629		0.1400	2.18	0.0304	
Week 24	0.1192	2.97	0.0032		0.0997	1.97	0.0502		0.1604	2.40	0.0177	
LDL-C												
Baseline	0.1714	0.96	0.3403	< 0.0001	-0.0130	-0.05	0.9579	< 0.0001	0.5128	2.01	0.0468	< 0.0001
Week 12	-0.1372	-0.75	0.4545		-0.1310	-0.52	0.6028		-0.0671	-0.26	0.7981	
Week 24	-0.8059	-4.34	< 0.0001		-0.8969	-3.57	0.0005		-0.6805	-2.50	0.0135	
Total cholesterol												
Baseline	0.7050	3.53	0.0005	< 0.0001	0.7648	2.90	0.0041	< 0.0001	0.6929	2.23	0.0269	0.0014
Week 12	0.3868	1.89	0.0598		0.3381	1.25	0.2121		0.3953	1.24	0.2169	
Week 24	-0.4585	-2.20	0.0281		-0.4255	-1.57	0.1171		-0.5923	-1.77	0.0780	
Triglyceride												
Baseline	0.1105	0.79	0.4273	0.0191	0.2382	1.30	0.1951	0.0027	-0.0708	-0.33	0.7380	0.0775
Week 12	-0.0752	-0.53	0.5997		-0.3387	-1.79	0.0743		0.2574	1.18	0.2388	
Week 24	-0.3600	-2.47	0.0139		-0.4118	-2.17	0.0306		-0.3721	-1.62	0.1062	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. P-value is test for interaction between time and treatment group.

patients under prolonged clozapine administration, Carrizo *et al.*³⁴ found that metformin treatment have significant effect on reducing elevated level of insulin and the ratio of insulin to HDL-C, as well as improving the level of HDL-C. In a recent study, Xu *et al.*³⁵ examined a large cohort for the effects of metformin on metabolite profile and LDL-C in patients with type 2 diabetes, and found that lower concentrations of three metabolites all are associated with LDL-C in blood sample. However, in a multi-center, double-blind, placebo-controlled trial using metformin to reduce body weight gain in schizophrenia or bipolar patients treated with olanzapine, Baptist *et al.*³⁶ reported that metformin could improve weight gain, but not lipid profile. This inconsistency may be due to several other factors such as the heterogeneity in patients because of a multi-center study design and shorter treatment period (12 weeks).

The effects of metformin treatment on reducing insulin or insulin resistance, and dyslipidemia occurred in a time-sequence manner. We observed that metformin treatment effects on weight gain and insulin resistance were significant at week 12, which is also the same for HDL-C. However, its effect on lipid profile such as LDL-C, total cholesterol and triglycerides did not appear until the end of trial at week 24. This is interesting, and suggests that metformin treatment effect on LDL-C, total cholesterol and triglycerides appear after the decrease in insulin resistance. That may be one of the reasons to explain why the previous study with 12-week trial did not find a significant effect of metformin treatment on LDL-C level.³⁶ There have been evidences showing that high insulin resistance is associated with increased cholesterol synthesis and decreased absorption in high-risk vascular patients who were not on lipid-lowering therapy³⁷ or in normoglycemic men.³⁸ This may explain that both insulin resistance and dyslipidemia are believed to be risk factors for cardiovascular disease.^{39,40} That metformin treatment improves insulin resistance and lipid profile may provide an evidence for an approximate causal relationship between reducing insulin resistance and improving lipid profile in schizophrenia patients treated with antipsychotics.

The evidence that metformin treatment improve the lipid profile in schizophrenia patients is to a certain degree

independent of insulin resistance. After controlling for insulin resistance index in the regression model, metformin treatment still have significant effect on reducing the level of LDL-C, total cholesterol and triglycerides, although it is known that the metformin treatment affect insulin resistance, which high level of insulin resistance index has been associated with increased cholesterol synthesis precursors and decreased absorption markers.^{37,38} In contrast, metformin treatment effect on improvement of HDL-C was mediated through the insulin resistance, as that after we controlled for insulin resistance index in the analysis, treatment effect was no longer significant. We should point out that among four lipid measurements, HDL-C were independent of LDL-C, total cholesterol and triglyceride. However, we did not observe metformin treatment effect on fasting glucose.

Our study showed that the reduced insulin resistance explain the improvement of HDL-C, but may not fully explain its effect on other lipids such as LDL-C, total cholesterol and triglyceride. The molecular mechanisms underlying metformin action appear related to its activation of the energy sensor AMP-activated protein kinase.^{41,42} Metformin is transported into hepatocytes mainly through organic cation transporter 1, leading to inhibit mitochondrial respiration chain (complex I), and then causing a decrease in energy availability in cell. The decrease in energy availability is balanced by reducing energy consumption, in particularly reduced gluconogenesis in the liver. This is mediated through signaling and metabolic flux effects that results from (1) a decrease in ATP and increase in AMP concentration, which directly contribute to the inhibition of gluconogenesis, and (2) the increased AMP levels function as a key signaling mediator that inhibits (cyclic adenosine 3',5'-monophosphate protein kinase A and FBPase, but activates AMP-activated protein kinase. As a result, inhibition of cyclic adenosine 3',5'-monophosphate protein kinase A and FBPase lead to decrease in glucose production; whereas activation of AMP-activated protein kinase causes a decrease in lipid and cholesterol synthesis.⁴¹ This mechanism may explain that metformin treatment can attenuate the altered level of both insulin resistance and lipid independently. A recent analysis of genomics and metabolomic data provided an empirical support in humans that reduced levels in three metabolites

(acyl-alkyl phosphatidylcholines) are consistently lower in type 2 diabetes mellitus patients treated with metformin, and they all were also associated with lowered blood level of LDL-C. The variations in these three metabolites were significantly associated with genetic variants at 17 genes including *FADS1* and *FADS2*, which are controlled by AMP-activated protein kinase.³⁵

Possible limitations

Our study should be read with some limitations. First, this study was based on schizophrenia patients treated with four different antipsychotic drugs including clozapine, olanzapine, risperidone and sulpiride. Previous study has shown that overall the type of medications affect the total cholesterol, triglyceride and prolactin significantly.⁴³ Unfortunately, we were unable to assess this effect by type of medication because of the smaller sample size in our study. Second, we did not monitor the level of prolactin, which is one of adverse effects induced by antipsychotics.⁴⁴ As most of typical and atypical antipsychotic medications block the dopamine D₂ receptor to help reducing the excess level of dopamine, which prevents excess prolactin secretion from the pituitary gland. Antipsychotic medication may lead to elevated level of prolactin in plasma.⁴⁵ In addition, we did not monitor serum B₁₂ and folate levels, although our laboratory tests did indicate that there was no decline in hemoglobin levels in any of the patients. Finally, we did not examine pharmacokinetic interactions between antipsychotics and metformin, nor monitor drug clearance. Metformin is unlikely to have interactions with antipsychotics because it is not metabolized and does not inhibit the metabolism of other drugs. Evidence has shown that slower metabolizer of risperidone may have a better treatment response in symptoms.³¹ This may affect antipsychotic drug response at least for risperidone.

In conclusion, despite these limitations, this study has shown clearly that the addition of metformin to antipsychotics is a potential treatment to attenuate dyslipidemia in patients with schizophrenia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

J-P Zhao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: R-R Wu and J-P Zhao. Acquisition of data: R-R Wu, J-P Zhao, J-J Ou and P Shao. Analysis and interpretation of data: R-R Wu and F-Y Zhang. Drafting of the manuscript: R-R Wu, F-Y Zhang and K-M Gao. Critical revision of the manuscript for important intellectual content: R-R Wu, J-P Zhao, F-Y Zhang, K-M Gao, J-J Ou, H Jin and P Shao. Statistical analysis: R-R Wu, F-Y Zhang and PK Chan. Obtained funding: R-R Wu. Administrative, technical or material support: R-R Wu, J-P Zhao, J-J Ou and P Shao. Study supervision: R-R Wu and J-P Zhao.

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