Effects of Adjunctive Metformin on Metabolic Traits in Nondiabetic Clozapine-Treated Patients With Schizophrenia and the Effect of Metformin Discontinuation on Body Weight: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: Many studies have shown that metformin can decrease body weight and improve metabolic abnormalities in patients with schizophrenia. Whether or not the beneficial effects can be sustained after discontinuation of metformin needs to be evaluated. We conducted a 24-week randomized, double-blind, placebo-controlled study to evaluate the effect of metformin on metabolic features in clozapine-treated patients with schizophrenia and followed their body weight after stopping the intervention for at least 24 weeks.

Method: The study was conducted between September 2008 and July 2011. We recruited patients with *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder who had been taking clozapine for more than 3 months, were overweight or obese, or fulfilled at least 1 criteria of metabolic syndrome. Eligible patients were randomized to receive metformin 1,500 mg/d or placebo. We followed metabolic features at baseline and at weeks 2, 4, 8, 16, and 24 and rechecked body weight when the patients stopped the trial after at least 24 weeks.

Results: A total of 55 subjects (28 in the metformin and 27 in the placebo group) were enrolled. There were no significant differences in all baseline characteristics between the 2 groups, except that patients in the metformin group had higher fasting plasma glucose levels ($P = .03$). After the 24-week intervention, body weight ($P < .0001$), body mass index ($P < .0001$), fasting plasma glucose ($P < .0001$), high-density lipoprotein cholesterol ($P = .03$), insulin level ($P = .01$), and homeostasis model assessment index ($P = .02$) had significant changes in the metformin group. At the end of the intervention, 8 patients (28.57%) lost more than 7% of their body weight in the metformin group. Mean body weight returned to baseline after patients stopped the intervention in the metformin group.

Conclusions: Metformin can significantly reduce body weight and reverse metabolic abnormalities in clozapine-treated patients with schizophrenia and preexisting metabolic abnormalities. However, the beneficial effects of metformin on body weight disappeared after discontinuing this medication.

Trial Registration: ClinicalTrials.gov identifier: NCT01300637

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Clozapine is the most effective agent available for treatment-resistant schizophrenia.[1,2] However, it is also one of the medications with the greatest propensity to induce body weight gain and metabolic abnormalities among all available antipsychotics.[3,4] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) phase-3 study[5] revealed that patients receiving clozapine increased body weight and blood levels of glucose, triglycerides, and glycosylated hemoglobin. Other longitudinal studies[6,7] also found that 36.6% and 43% of clozapine-treated patients were diagnosed with diabetes mellitus during 5-year and 10-year follow-up, respectively. In addition, the prevalence of metabolic syndrome in clozapine-treated patients was at least 2.5 times that in the general population.[8] Metabolic abnormalities not only result in substantial morbidity and mortality[4,9] but also affect functional outcome,[10] self-esteem,[11] and compliance.[12] Therefore, it is important to control metabolic abnormalities in clozapine-treated patients with schizophrenia.

Metformin, which is prescribed for patients with non–insulin-dependent diabetes mellitus to control blood glucose levels, has been reported to reduce body weight in subjects with insulin resistance.[13,14] In a 3-year follow-up study,[15,16] metformin was shown to reduce the development of metabolic syndrome and diabetes mellitus in individuals with impaired glucose tolerance, though results were less robust than intensive lifestyle intervention. One recent report[17] reviewed the effectiveness of 15 medications to attenuate antipsychotic-related weight gain and metabolic abnormalities. Among 5 effective medications, which included metformin D-fenfluramine, sibutramine, topiramate, and reboxetine, metformin is the most effective one. Although several double-blind, placebo-controlled studies have evaluated the effect of metformin on metabolic features in patients receiving atypical antipsychotics,[18–24] most of the intervention ranged from 12 to 14 weeks (except for a study by Wu et al,[24] in which intervention was 6 months), and only 1 study specifically recruited clozapine-treated patients.[21] Metformin has been shown to sustain its effect on reducing body weight and improving lipid profiles among subjects with impaired glucose tolerance in long-term follow-up.[15,16,25] Recently, Wu et al[24] reported that women with first-episode schizophrenia and antipsychotic-induced amenorrhea reduced their body mass index (BMI) after receiving 6 months of metformin treatment. As a result, we sought to examine whether or not the long-term use of metformin could sustain its beneficial effects on body weight and metabolic features in clozapine-treated patients with preexisting metabolic abnormalities. Furthermore, there

has been no study to date that evaluates the subsequent changes in body weight and metabolic features after discontinuing metformin intervention. Hence, the study aim was 2-fold: first, to assess metformin's effect on body weight and metabolic features in clozapine-treated patients with schizophrenia and preexisting metabolic abnormalities in a 24-week randomized, double-blind, placebo-controlled trial; and second, to follow up on the patients' body weight after completing the metformin intervention for at least 24 weeks. We hypothesized that metformin would have beneficial effects on metabolic profiles; however, the effects of the medication would disappear after its discontinuation.

METHOD

The current trial of adjunctive metformin for clozapine-treated patients with schizophrenia and preexisting metabolic abnormalities was conducted in Taipei Medical University-Wan Fang Hospital (TMU-WFH) and Taipei City Psychiatric Center (TCPC), Taiwan, between September 2008 and July 2011, and was approved by the corresponding institutional review boards. The protocol was registered on www.clinicaltrials.gov (NCT01300637).

To be eligible for the study, patients needed to be fully capable of comprehending the study's purpose, procedure, treatment, risk and possible benefits, alternative treatment, and their right to refuse to participate in this study. Patients' competence to consent was determined by their in-charge psychiatrists. If their in-charge psychiatrists were research psychiatrists, another psychiatrist was assigned to evaluate the patients' competence. We obtained written informed consent from all patients before enrolling them into the study.

Subjects

We screened 127 patients with *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder, who were aged 20 to 65 years and had taken clozapine for at least 3 months, in outpatient clinics of TMU-WFH and TCPC (n = 109) and in rehabilitation wards of TCPC (n = 18). Screened patients were weighted on a digital electronic scale, and weight was recorded to the nearest 0.1 kg. Sitting blood pressure and anthropometric measurements were measured. Two blood pressure measurements were made 30 seconds apart on the right arm after the participant sat and rested for 5–10 minutes. A third blood pressure measurement was made when the first 2 blood pressure readings differed by more than 10 mm Hg. The mean of the 2 closest readings was calculated and used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing using a tape with a spring-loaded mechanism to standardize tape tension during measurement. BMI was calculated as weight in kilograms divided by the square of the height in meters.

Overnight fasting blood was collected for fasting plasma glucose and serum lipid levels analyses. Triglycerides and fasting plasma glucose were measured by an automated system. High-density lipoprotein cholesterol (HDL-C) level was measured by electrophoresis. In addition, basic serum biochemistry, including blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase, were measured. A urine pregnancy test was performed for potentially pregnant female patients.

In this study, we adopted the International Diabetes Federation Task Force Criteria of metabolic syndrome to ascertain the diagnosis of metabolic syndrome.[26] Three or more of the following 5 criteria were required: (1) abdominal obesity (waist circumference greater than 90 cm in men and greater than 80 cm in women); (2) fasting serum triglyceride levels of 150 mg/dL or above; (3) fasting serum HDL-C levels less than 40 mg/dL in men, or less than 50 mg/dL in women; (4) systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or current treatment with antihypertensive medication; and (5) a fasting plasma glucose level of 100 mg/dL or above, or current treatment with antihyperglycemic medication. Insulin resistance was calculated using the homeostasis model assessment insulin-resistance (HOMA-IR: fasting glucose [mmol/L] × fasting insulin [mU/L] / 22.5).[27]

Patients were invited to participate in the 24-week, randomized, double-blind, placebo-controlled intervention if they met BMI ≥ 24, or 1 or more metabolic abnormalities, which were defined in the previous paragraph. The exclusion criteria were history of diabetes mellitus; current use of hypoglycemic or hypolipidemic agents; women who are pregnant; known allergy or contraindicated to metformin, such as creatinine > 1.4 ng/dL; abnormal liver function test; or chronic cardiopulmonary insufficiency. We also excluded patients with fasting plasma glucose levels ≥ 126 mg/dL, which fulfilled the diagnosis of diabetes mellitus and needed further intervention.

Recruited patients' data were collected from clinical interviews and their medical records, which included demographic characteristics and clinical information, such as diagnosis, age at onset of schizophrenia or schizoaffective disorder, clozapine initiation, and current clozapine dose. We also assessed their symptoms using the Positive and Negative Syndrome Scale (PANSS).[28] Because many patients had taken clozapine for a long time, and many had changed the location of the hospital from which they received medications, we could not know the exact reason for using clozapine from their medical records.

Study Design

Recommendations with regard to a healthy diet and exercise to control body weight were provided by research assistants at the beginning of the intervention, but not during the follow-up visits. The clozapine dosage was maintained unchanged throughout the intervention.

Eligible patients were randomized to either the metformin or placebo group. To ensure the concealment of the randomization assignment, metformin and identical-appearing placebo were provided by coded containers. The randomization allocation was conducted by a research assistant who was blind to the status of participants. Patients, caregivers, and investigators were all masked to

Clinical Points

- Metformin can effectively improve metabolic-related features in nondiabetic clozapine-treated patients with schizophrenia.
- The beneficial effect of metformin on reducing body weight disappears after discontinuation.

the assignment. The assignments were decoded at the end of intervention.

In our previous trial,[29] we found that metformin 1,500 mg/d can effectively improve some metabolic features in patients treated with olanzapine. Therefore, we set the target dose of metformin at 500 mg 3 times per day in the current study. In the first week of intervention, each day we provided 500 mg of metformin or placebo at the patients' morning and evening meals. Then 500 mg of metformin or placebo was titrated to 3 times with their meal at the second week, unless subjects could not tolerate side effects induced by intervention. For those who could not tolerate metformin 500 mg 3 times per day at week 4, the tolerable metformin dose at week 4 was kept during the following intervention period.

Table 1. Baseline Characteristics of Non-Diabetic Clozapine-Treated Patients With Schizophrenia Entering the Intervention[a]

Characteristic	Metformin (n = 28)	Placebo (n = 27)	*P* Value
Male/female, n/n	13/15	15/12	.50
Age, mean (SD), y	41.8 (7.2)	41.4 (10.2)	.85
Age at onset, mean (SD), y	21.2 (5.8)	20.8 (5.3)	.76
Clozapine dose, mean (SD), mg/d	252.7 (102.6)	282.4 (99.2)	.28
Duration of clozapine use, mean (SD), mo	68.3 (54.2)	61.1 (48.1)	.59
Body weight, mean (SD), kg	69.1 (13.7)	67.2 (9.6)	.55
BMI, mean (SD), kg/m^2	25.9 (3.9)	25.7 (4.3)	.87
Waist circumference, mean (SD), cm	89.8 (11.1)	88.5 (9.8)	.63
Blood pressure, mean (SD), mm Hg			
Systolic	114.8 (13.5)	116.2 (16.0)	.71
Diastolic	77.6 (11.4)	75.5 (10.8)	.50
Fasting plasma glucose, mean (SD), mg/dL	102.2 (14.1)	94.2 (12.6)	**.03***
Triglyceride, mean (SD), mg/dL	147.3 (65.0)	122.5 (73.5)	.19
HDL-C, mean (SD), mg/dL	47.6 (16.6)	47.0 (14.3)	.88
Insulin, mean (SD), mU/L	8.6 (5.8)	8.0 (6.3)	.71
HOMA-IR, mean (SD)	2.3 (1.7)	1.8 (1.4)	.31

[a]Values in bold represent a significant (*$P < .05$) difference between groups.
Abbreviations: BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment-insulin resistance.

Follow-Up Assessments

Recruited patients were followed at weeks 2, 4, 8, 16, and 24. At each follow-up visit, all baseline evaluations, such as physical and laboratory examinations, were repeated. The laboratory tests were performed in the morning after an overnight fasting. In addition, we assessed their PANSS scores at week 24. After patients completed the trial for at least 24 weeks, their body weight was measured again.

Statistical Analysis

We used descriptive statistics for baseline clinical characteristics, and *t* test to examine the differences in these characteristics between the metformin and the placebo groups. We adopted the-last-observation-carried-forward approach to deal with the missing data, assuming no change in the missing values of metabolic-related indices after the event of dropout. Patients who stayed in the intervention at least 4 weeks were included into analyses. To investigate whether repeated measures collected in a longitudinal manner were changing over time, we first used paired *t* test to examine differences between baseline and follow-up measures. Repeated measure analyses were conducted using 1-way within-subjects analysis of variance to detect within-groups effect ($df = 5$) and using 2-way within-subjects analysis of variance to examine group effect ($df = 1$, between groups), time effect ($df = 5$, within subjects), and interaction effect ($df = 5$, *time* × *group*) in the metabolic syndrome–related indices over time. In addition, we hypothesized that the proportion of significant body weight loss and reversing metabolic abnormalities in the metformin group was greater than that in the placebo group. Thus, difference test in proportions was conducted for the number (or proportion) of patients who experienced more than a 7% body weight loss and reversed metabolic abnormalities in each time-point of follow-up compared to baseline. All analyses were conducted using statistical software R version 2.11.1 (R Project, University of Auckland, New Zealand, http://www.r-project.org/).

RESULTS

Fifty-eight of 127 screened patients fulfilled the intervention criteria. Three of 58 patients declined to enter the intervention phase, because of their unwillingness to add medications in this trial. A total of 55 subjects were recruited into this randomized, double-blind, placebo-controlled trial. Before the trial, we could find no statistically significant correlations between clozapine dose and values of metabolic-related indices (data not shown). Twenty-eight (5 inpatients and 23 outpatients) and 27 (5 inpatients and 22 outpatients) subjects were randomly assigned to the metformin and the placebo groups, respectively. Table 1 shows their demographic and clinical characteristics. There were no significant differences with regard to all baseline characteristics between these 2 groups, except that patients in the metformin group had higher fasting plasma glucose levels than those in the placebo group ($P = .03$).

Table 2 demonstrates changes of metabolic features in the metformin group and the placebo group over the 24-week intervention. We observed statistically significant time effect within subjects over time in body weight ($P < .0001$), BMI ($P < .0001$), fasting plasma glucose ($P = .0001$), HDL-C ($P = .004$), insulin level ($P = .02$), and HOMA-IR ($P = .01$). We also observed significant group × time interaction in body weight ($P < .0001$) and BMI ($P < .0001$). However, no significant group effect (ie, between groups) in any metabolic-related index was observed. In addition, significant differences in body weight ($P < .0001$), BMI ($P < .0001$), fasting plasma

Table 2. Metabolic Features During 24-Week Follow-Up in the Metformin Group and the Placebo Group[a]

Trait, Group	Baseline, Mean (SD)[b]	2-Week Follow-Up, Mean (SD)[b]	4-Week Follow-Up, Mean (SD)[b]	8-Week Follow-Up, Mean (SD)[b]	16-Week Follow-Up, Mean (SD)[b]	24-Week Follow-Up, Mean (SD)[b]	Between Groups, *df* = 1 (group effect)[c]		Within Subject, *df* = 5 (time effect)[d]		Group × Time Effect,[e] *df* = 5	
							F Value	*P* Value	F Value	*P* Value	F Value	*P* Value
Body weight, kg							0.04	.85	12.32	**<.0001**	10.84	**<.0001**
Metformin	69.1 (13.7)	68.4 (13.0)	**68.0 (13.0)***	**67.8 (12.9)***	**66.9 (13.3)***	**65.9 (12.6)***						
Placebo	67.2 (9.6)	66.9 (9.4)	67.0 (9.5)	67.4 (9.3)	67.1 (9.0)	67.0 (8.7)						
BMI, kg/m^2							0.08	.78	10.85	**<.0001**	11.09	**<.0001**
Metformin	25.9 (3.9)	25.7 (3.7)	**25.5 (3.7)***	**25.4 (3.7)***	**25.1 (3.8)***	**24.7 (3.6)***						
Placebo	25.7 (4.3)	25.6 (4.2)	25.6 (4.4)	25.8 (4.4)	25.7 (4.3)	25.7 (4.2)						
Waist circumference, cm							0.12	.73	0.86	.51	1.07	.38
Metformin	89.8 (11.1)	**88.1 (10.7)***	**87.6 (10.6)***	**87.7 (9.8)***	88.6 (11.5)	88.3 (12.0)						
Placebo	88.5 (9.8)	88.1 (10.1)	88.2 (10.0)	89.0 (10.1)	88.4 (9.6)	89.0 (9.4)						
Systolic blood pressure, mm Hg							0.003	.96	2.08	.07	1.19	.32
Metformin	114.8 (13.5)	**122.1 (12.2)***	120.0 (13.0)	116.5 (13.6)	112.7 (20.6)	114.0 (22.2)						
Placebo	116.2 (16.0)	115.6 (12.6)	119.7 (15.5)	118.0 (12.2)	115.9 (13.5)	115.6 (18.9)						
Diastolic blood pressure, mm Hg							0.09	.76	1.77	.12	0.51	.77
Metformin	77.6 (11.4)	79.9 (9.9)	78.9 (9.6)	76.6 (9.6)	76.8 (7.6)	74.8 (8.6)						
Placebo	75.5 (10.8)	77.9 (10.3)	78.7 (10.1)	77.5 (9.9)	75.3 (9.6)	76.3 (11.0)						
Fasting plasma glucose, mg/dL							0.03	.87	5.21	**.0001**	2.18	.06
Metformin	102.2 (14.1)	**94.8 (10.7)***	**96.1 (12.4)***	**92.5 (10.5)***	**89.1 (11.2)***	**93.5 (12.7)***						
Placebo	94.2 (12.6)	**99.3 (14.3)***	98.8 (15.7)	93.7 (22.9)	93.0 (19.4)	**99.9 (18.0)***						
Triglyceride, mg/dL							0.01	.92	0.31	.91	0.92	.47
Metformin	147.3 (65.0)	**128.5 (49.4)***	127.5 (63.3)	**120.6 (48.3)***	130.8 (62.6)	126.8 (47.4)						
Placebo	122.5 (73.5)	130.8 (93.1)	138.0 (89.1)	130.7 (111.8)	132.3 (151.6)	126.9 (79.4)						
HDL-C, mg/dL							0.007	.94	3.52	**.004**	1.70	.13
Metformin	47.6 (16.6)	45.7 (15.7)	46.5 (15.5)	**44.3 (14.6)***	**44.5 (14.2)***	**44.2 (14.6)***						
Placebo	47.0 (14.3)	48.0 (14.7)	46.1 (14.9)	46.1 (15.2)	45.1 (17.6)	46.4 (14.2)						
Insulin, mU/L							2.50	.12	2.74	**.02**	1.94	.09
Metformin	8.6 (5.8)	**7.3 (6.3)***	7.0 (4.1)	**5.3 (3.2)***	**4.9 (2.9)***	6.8 (5.5)						
Placebo	8.0 (6.3)	7.8 (5.3)	9.2 (6.3)	8.5 (7.2)	8.4 (5.8)	12.4 (12.8)						
HOMA-IR							0.39	.54	3.01	**.01**	1.55	.17
Metformin	2.3 (1.7)	**1.8 (1.7)***	1.7 (1.1)	**1.2 (0.8)***	**1.1 (0.8)***	1.7 (1.6)						
Placebo	1.8 (1.4)	2.0 (1.6)	2.4 (2.0)	2.1 (1.9)	2.0 (1.5)	3.3 (3.8)						

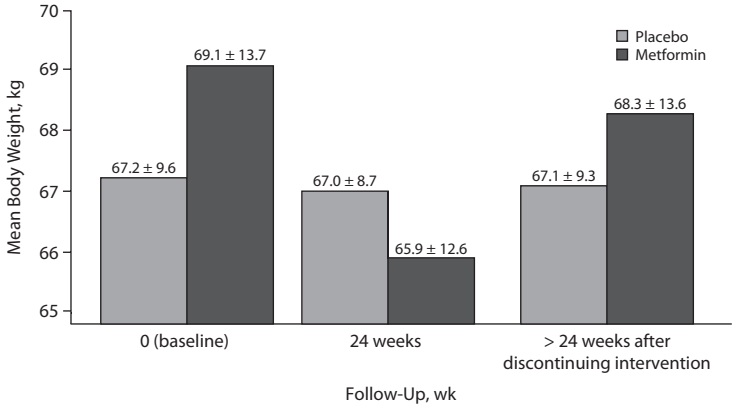
[a]Analyses were based on 55 subjects (28 in the metformin group and 27 in the placebo group).
[b]Difference tests between baseline and follow-up in the metformin group and the placebo group used paired *t* test. Values in bold represent a significant (*$P < .05$) difference between baseline and follow-up in a group.
[c]Between-groups effect (2-way within-subjects ANOVA with $df = 1$) represents that there is significant difference in the metabolic syndrome–related variable among baseline and follow-up steps between the metformin group and the placebo group.
[d]Within-subject effect ($df = 5$) indicates that there is a significant time effect, in other words, the groups do change in the metabolic syndrome–related variable over time.
[e]Group × time effect ($df = 5$) stands for significant group × time interaction.
Abbreviations: ANOVA = analysis of variance, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment-insulin resistance.

Table 3. Prevalence of Metabolic Syndrome in the Metformin Group and the Placebo Group[a]

Metabolic Abnormality, Group	Baseline, n (%)[b]	2-Week Follow-Up, n (%)[b]	4-Week Follow-Up, n (%)[b]	8-Week Follow-Up, n (%)[b]	16-Week Follow-Up, n (%)[b]	24-Week Follow-Up, n (%)[b]
Abdominal obesity						
Metformin	18 (64.29)	17 (60.71)	14 (50.00)	15 (53.57)	16 (57.14)	15 (53.57)
Placebo	13 (48.15)	11 (40.74)	13 (48.15)	11 (40.74)	13 (48.15)	13 (48.15)
Hypertriglyceridemia						
Metformin	14 (50.00)	**9 (32.14)***	**7 (25.00)****	**8 (28.57)***	**8 (28.57)***	**7 (25.00)****
Placebo	7 (25.93)	8 (29.63)	9 (33.33)	8 (29.63)	5 (18.52)	8 (29.63)
Low fasting HDL-C						
Metformin	16 (57.14)	15 (53.57)	14 (50.00)	17 (60.71)	17 (60.71)	17 (60.71)
Placebo	11 (40.74)	12 (44.44)	13 (48.15)	13 (48.15)	15 (55.56)	14 (51.85)
High blood pressure						
Metformin	8 (28.57)	9 (32.14)	6 (21.43)	8 (28.57)	5 (17.86)	5 (17.86)
Placebo	8 (29.63)	6 (22.22)	10 (37.04)	7 (25.93)	7 (25.93)	9 (33.33)
High fasting glucose						
Metformin	16 (57.14)	**9 (32.14)****	**8 (28.57)****	**5 (17.86)*****	**4 (14.29)*****	**9 (32.14)****
Placebo	11 (40.74)	14 (51.85)	14 (51.85)	8 (29.63)	10 (37.04)	8 (29.63)
Metabolic syndrome						
Metformin	13 (46.43)	12 (42.86)	**7 (25.00)***	**8 (28.57)***	**8 (28.57)***	9 (32.14)
Placebo	9 (33.33)	6 (22.22)	13 (48.15)	8 (29.63)	8 (29.63)	9 (33.33)

[a]Analyses were based on 55 subjects (28 in the metformin group and 27 in the placebo group).
[b]Difference change was calculated based on the difference between baseline and 24-week follow-up without taking medication. Values highlighted in bold (*P < .05, **P < .01, ***P < .001) represent a significant difference in the proportion test under the null that the proportion at baseline is less than that at follow-up.
Abbreviation: HDL-C = high-density lipoprotein cholesterol.

Figure 1. Trends of Body Weight (Mean) Changes in the Metformin Group and the Placebo Group at Baseline, 24-Week Follow-Up, and >24-Week Follow-Up After Discontinuing Intervention (mean ± SD)



glucose (P < .0001), HDL-C (P = .03), insulin level (P = .01), and HOMA-IR (P = .02) were exhibited within the metformin group, and in fasting plasma glucose (P = .02) and HDL-C levels (P = .03) within the placebo group (see Supplementary eTable 1).

The trends of the metabolic-related indices changes at time of baseline and weeks 2, 4, 8, 16, and 24 in both groups can be also seen in Table 2. Compared to their baseline data, patients in the metformin group had a mean (SD) body weight change of −3.2 (3.1) kg (P < .001), but those in the placebo group had a relatively stable body weight at the end of the 24-week intervention; the mean (SD) BMI change was −1.2 (1.1) kg (P < .001) in the metformin group and 0 (0.7) kg (not significant) in the placebo group. There were also significant changes in fasting plasma glucose and HDL-C, with a mean (SD) of −8.7 (16.6) mg/dL and −3.3 (7.7) mg/dL, respectively, in the metformin group (both P values < .05). No other significant changes were noted between baseline and 24-week follow-up in both groups. (Detailed data are shown in Supplementary eTable 1.)

Table 3 shows the prevalence of metabolic syndrome in both groups over time. We found that metformin significantly reduced the proportion of patients having hypertriglyceridemia and high fasting plasma glucose since week 2. The prevalence of metabolic syndrome significantly decreased at week 4, 8, and 16 in the metformin group (P < .05), but did not significantly change in the placebo group.

More than 7% body weight loss is considered clinically significant body weight loss. The numbers of patients who decreased more than 7% of their body weight compared with their baseline body weight in the metformin group were 1 (3.57%), 1 (3.57%), 1 (3.57%), 3 (10.71%), and 8 (28.57%) at weeks 2, 4, 8, 16, and 24, respectively. None of the patients had significant body weight loss in the placebo group.

We followed up on the body weight of patients after they discontinued intervention for at least 24 weeks, from 24 to 80 weeks, with a mean (SD) of 33.2 (15.7) weeks. Figure 1 shows mean body weight changes at baseline, 24 weeks, and follow-up after stopping intervention. Although metformin significantly reduced mean body weight, patients' body weight returned to baseline levels after they stopped taking metformin (baseline vs follow-up after stopping intervention, P = .30, paired t test). There was no significant body weight change in the placebo group (baseline vs follow up after stopping intervention, P = .86, paired t test).

All patients could tolerate 1,500 mg of metformin. No severe adverse effects were noted, such as lactic acidosis, throughout

the 24-week intervention. Seven patients complained of nausea and vomiting in the metformin and 3 in the placebo group; 9 complained of diarrhea in the metformin and 5 in the placebo group. There was no significant difference in reporting adverse effects between the metformin and the placebo groups.

Recruited patients' clinical status, ie, inpatient or outpatient, did not change throughout the study. The PANSS scores did not significantly change, with a mean (SD) of 59.1 (14.1) at baseline and 52.5 (19.0) at week 24 in the metformin group, and 61.3 (15.3) at baseline and 59.2 (21.4) at week 24 in the placebo group.

DISCUSSION

In this 24-week randomized, double-blind, placebo-controlled trial, we found that metformin could significantly reduce body weight and improve metabolic features in clozapine-treated patients with schizophrenia and preexisting metabolic abnormalities. Metformin's beneficial effect on metabolic features could appear at as early as week 2 and sustain as long as 24 weeks. In addition, metformin reversed metabolic syndrome, primarily due to its effect on triglyceride level and fasting plasma glucose. However, the beneficial effects on body weight disappeared after patients stopped taking metformin for at least 24 weeks. No serious adverse effects were noted throughout the intervention.

In our study, the mean duration of clozapine use was more than 5 years in the metformin and the placebo groups. Long-term clozapine use had led these patients' body weight to plateau, which was shown by no significant body weight change during the intervention period and even 24 weeks after the intervention in the placebo group (Figure 1). However, metformin intervention could reduce body weight, which took place at the plateau of weight gain. Several studies[18,20–23] have reported that metformin could reduce body weight in patients treated with antipsychotics. The magnitude of weight reduction varied from 1.4 to 3.2 kg in 12- to 14-week trials. Our results not only supported the weight reduction effect of metformin in clozapine-treated patients with schizophrenia but also showed that the effect could last as long as 24 weeks. Our results were similar to those in another 6-month trial,[24] in which metformin could reduce body weight and BMI by a mean of 2.3 kg and 0.93 kg, respectively, in women with first-episode schizophrenia. Moreover, we found the proportion of more than 7% of body weight loss obviously increased during 16–24 weeks of metformin treatment. In a large trial of subjects with impaired glucose tolerance, metformin could effectively reduce the incidence of diabetes mellitus[15] and metabolic syndrome[16] in a 3-year follow-up, and metformin's effect on decreasing body weight could last as long as 10 years.[25] Therefore, whether long-term (longer than 6 months) metformin use can prevent or reverse metabolic abnormalities in patients with schizophrenia is worth studying.

Our study showed that metformin can effectively decrease fasting plasma glucose, fasting insulin level, and HOMA-IR. The results are similar to those in previous studies in which either preventing insulin increase[20,22] or decreasing insulin resistance[21,23,24] were noted. Therefore, metformin is considered to be one of the medications to prevent diabetes mellitus in high-risk groups.[30,31] However, the effects of metformin on other metabolic profiles are controversial. We found that metformin could decrease waist circumference in the first 8 weeks, but the effect could not persist in the following weeks. A decrease in waist circumference was also found in Wu and colleagues' study,[23] but not in others.[18,21,22] Regarding lipid profiles, HDL-C decreased in the metformin group, but not in the placebo group. One study had a similar finding that HDL-C decreased after metformin treatment,[20] but another study found it increased.[21] Although mean HDL-C levels significantly decreased in the metformin group in our study, the prevalence of fulfilling low HDL-C criteria did not increase. On the contrary, the prevalence of having hypertriglyceridemia decreased in the metformin group, though mean triglyceride level did not significantly change. In addition, metformin's lowering of fasting plasma glucose level results in a decreased prevalence of high fasting plasma glucose. Therefore, the prevalence of metabolic syndrome significantly decreased at weeks 4, 8, and 16 (not significant at 24 weeks) in the metformin group, but did not significantly change in the placebo group throughout the intervention. The results were similar to our previous open trial, in which half of the patients with metabolic syndrome at baseline no longer met the criteria for metabolic syndrome after 12 weeks of metformin treatment.[29] Gangale et al[32] also demonstrated that metformin can decrease the prevalence of metabolic syndrome in overweight patients with polycystic ovarian syndrome.

Until now, no published study in the psychiatric field explored whether the effects of metformin on metabolic features could be sustained after patients stop taking it. In the follow-up after patients stopped the intervention for at least 24 weeks, we found that mean body weight returned to baseline in the metformin group, but remained unchanged in the placebo group. Although metformin's effect on reducing body weight can persist as long as 10 years,[25] our data suggest that the effect could not be sustained after patients stopped taking this medication.

Small sample size limits the generalization of our current study. Furthermore, there are several other study limitations that should be noted. First, because we did not record characteristics of patients' lifestyles, such as physical activity and diet, we could not know the amplitude of physical activity and appetite changes, which may affect metabolic outcomes, after using metformin or placebo. Second, because we only followed patients with regard to body weight after they stopped taking metformin or placebo, we could not know how other metabolic indices, such as glucose homeostasis and lipid profiles, changed after discontinuing intervention. Furthermore, the follow-up time point was at least 24 weeks after their discontinuation, so the time point when the body weight started to return to baseline is not clear. Third, medication adherence was not precisely recorded in both groups. In our follow-up visits, we inquired with patients' caregivers about patients' medication adherence.

Even though nearly all patients and their caregivers reported good medication adherence, we could not quantify these statements. Fourth, most of the study group used the target dose of metformin, ie, 1,500 mg/d. We could not know the dosing effect on metabolic profiles. Wu et al[22,23] found that even doses of metformin as low as 750 mg/d had a beneficial effect on metabolic profiles in patients with schizophrenia.

In conclusion, our study shows that up to 24 weeks of metformin can persistently reduce body weight and improve metabolic function, but the weight-reducing effects do not persist after cessation of metformin. Other studies of patients without psychosis show that chronic treatment with metformin can produce lasting effects for up to 10 years.[25] Because our own study and other studies have shown relatively mild side effects of metformin, a strategy for long-term metformin supplementation in clozapine-treated patients with schizophrenia and preexisting metabolic abnormalities is suggested. However, the definite efficacy of such a strategy has to be evaluated in longer-term studies.

Drug names: clozapine (Clozaril, FazaClo, and others), metformin (Glucophage, Glumetza, and others), olanzapine (Zyprexa and others), topiramate (Topamax and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Effects of Adjunctive Metformin on Metabolic Traits in Nondiabetic Clozapine-Treated Patients With Schizophrenia and the Effect of Metformin Discontinuation on Body Weight: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study

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List of Supplementary Material for the article

1. **Supplementary eTable 1** Difference test between baseline and follow-up (paired *t*-test) and difference test within group over time (one-way within-subjects ANOVA)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Tables

Table S1. Difference test between baseline and follow-up (paired t-test) and difference test within group over time (one-way within subjects ANOVA)

		Mean difference (s.d.)[a]					*p*-value[b]
Metabolic related traits	Group	Baseline vs. 2-week	Baseline vs. 4-week	Baseline vs. 8-week	Baseline vs. 16-week	Baseline vs. 24-week	Within group (df=5)
BW	Metformin	-0.7 (1.9)	**-1.1 (2.1)***	**-1.3 (2.2)****	**-2.2 (2.9)*****	**-3.2 (3.1)*****	**<0.0001**
	Placebo	-0.3 (1.2)	-0.2 (1.4)	0.2 (1.8)	-0.1 (1.8)	-0.2 (2.1)	0.72
BMI	Metformin	-0.2 (0.7)	**-0.4 (0.7)****	**-0.5 (0.8)****	**-0.8 (1.0)*****	**-1.2 (1.1)*****	**<0.0001**
	Placebo	-0.1 (0.4)	-0.1 (0.5)	0.1 (0.7)	0.0 (0.7)	0.0 (0.7)	0.52
WC	Metformin	**-1.7 (4.0)***	**-2.2 (4.6)***	**-2.2 (4.6)***	-1.2 (7.9)	-1.5 (10.3)	0.40
	Placebo	-0.3 (2.2)	-0.3 (3.2)	-0.6 (2.8)	-0.4 (3.6)	0.3 (4.5)	0.46
SBP	Metformin	**7.4 (10.3)*****	5.2 (16.9)	1.7 (11.8)	-2.0 (22.3)	-0.8 (23.5)	0.056
	Placebo	-0.6 (15.2)	3.5 (15.9)	1.8 (12.3)	-0.3 (12.7)	-0.7 (18.1)	0.61
DBP	Metformin	2.4 (11.5)	1.4 (13.6)	-0.9 (12.5)	-0.8 (14.1)	-2.8 (14.6)	0.25
	Placebo	2.4 (13.2)	3.2 (10.3)	2.0 (10.7)	-0.2 (10.2)	0.8 (13.1)	0.48
FPG	Metformin	**-7.4 (11.7)****	**-6.0 (15.4)***	**-9.7 (15.5)****	**-13.1 (12.4)*****	**-8.7 (16.6)***	**<0.0001**
	Placebo	**5.1 (9.6)***	4.6 (16.8)	-0.5 (20.9)	-1.5 (16.8)	5.7 (17.6)	**0.02**
TG	Metformin	**-18.8 (45.7)***	-19.8 (64.2)	**-26.7 (52.2)***	-16.5 (55.8)	-20.5 (53.8)	0.11
	Placebo	8.3 (72.3)	15.5 (55.7)	8.2 (84.9)	8.0 (128.2)	4.4 (46.0)	0.94
HDL-C	Metformin	-1.9 (6.4)	-1.1 (7.2)	**-3.3 (6.9)***	**-3.1 (7.5)***	**-3.3 (7.7)***	**0.03**
	Placebo	1.0 (6.3)	-0.8 (7.3)	-0.9 (5.2)	-2.2 (9.6)	-0.6 (5.5)	**0.03**
Insulin	Metformin	**-1.5 (3.4)***	-1.6 (6.3)	**-3.2 (5.0)****	**-3.7 (5.1)*****	-1.8 (6.4)	**0.01**
	Placebo	0.6 (5.9)	2.3 (6.4)	0.7 (5.7)	0.5 (5.4)	4.4 (12.7)	0.07

HOMA-IR	Metformin	**-0.6 (1.0)***	-0.6 (1.9)	**-1.0 (1.5)****	**-1.2 (1.6)*****	-0.6 (2.0)	**0.02**
	Placebo	0.4 (1.7)	0.8 (2.0)	0.3 (1.7)	0.2 (1.5)	1.5 (3.9)	0.06

[a] Mean difference represents the mean of baseline subtract the mean of follow-up. Difference tests between baseline and follow-up in the metformin group and the placebo group used paired *t*-test. Values in bold represent significant (i.e. $p<0.05$) difference between baseline and follow-up in groups.

[b] Difference tests within group are based on 28 subjects in the metformin group and based on 27 subjects in the placebo group using one-way within subjects ANOVA with df=5.

*$p<0.05$, **$p<0.01$, ***$p<0.001$.

Abbreviations: BMI = body mass index, BW = body weight, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment-insulin resistance, SBP = systolic blood pressure, TG = triglyceride, WC = waist circumference.