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Original Article

Clostridium butyricum CGMCC 0313.1 improves clinical outcomes of metabolic syndrome in schizophrenic patients

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Abstract: Objective: To primarily analyze the therapeutic effectiveness of *Clostridium butyricum* CGMCC 0313.1 (CB0313.1) in managing metabolic syndrome (MS) in patients with schizophrenia. Methods: A total of 100 schizophrenic patients with relatively stable conditions admitted were selected. Patients receiving CB0313.1 were assigned to the observation group (n=52), and the others undergoing lifestyle interventions without CB0313.1 were formed the control group (n=48). Additionally, changes in obesity indices, blood sugar (BS) data, lipid profiles, blood pressure (BP), oxidative stress markers, Positive and Negative Syndrome Scale (PANSS) scores, treatment efficacy, and quality of life were evaluated before and after 12 weeks of intervention. Results: After the intervention, the observation group presented significantly greater improvements in oxidative stress reduction, and overall therapeutic efficacy compared to the control group. In addition, the observation group showed more pronounced reductions in obesity indices, BS levels, lipid profiles, BP, and PANSS scores. However, improvements in quality-of-life were comparable between the two groups. Conclusion: CB0313.1 helps enhance the clinical management of MS in schizophrenic patients.

Keywords: *Clostridium butyricum* CGMCC 0313.1 (CB0313.1), schizophrenia, metabolic syndrome, therapeutic effect, life-style intervention

Introduction

Schizophrenia is a prevalent and severe psychiatric disorder associated with substantial disease burden and a high disability rate [1]. Metabolic syndrome (MS), characterized by dysregulation of protein, fat, and carbohydrate metabolism, is a risk factor for cardiovascular and cerebrovascular disease [2, 3]. Currently, up to 33.3% of adults globally are affected by MS, and individuals with schizophrenia are three times more likely to develop MS than the general population, with a rising prevalence [4-6]. Schizophrenic patients with MS often present with increased body mass index (BMI), elevated blood pressure (BP), and glucose-lipid metabolism disorders, which not only compromise patients' treatment compliance but also lead to poor prognosis [7]. At present, symptomatic treatment remains the primary treatment; however, it has obvious shortcomings, such as limited efficacy, delayed onset of action, and adverse reactions or interference with antipsychotic medications, undermining treatment effectiveness [8, 9]. Hence, it is necessary to develop safe and effective treatment schemes to restore the metabolic balance in schizophrenic patients with MS.

Lifestyle interventions for schizophrenic patients with MS typically comprise three core components: nutritional management, structured exercise regimens, and rehabilitative activities [10]. Evidence suggests that comprehensive lifestyle modification can help mitigate MS and improve glucose and lipid metabolism in these patients [11, 12]. Regulating gut microbiota, in particular, represents a novel therapeutic approach for managing MS in individuals with schizophrenia [13]. The gut microbiota play a key role in energy homeostasis and metabolic regulation, possibly influencing metabolic outcomes by modulating appetite-related hormones, enhancing glucose tolerance, and affecting hormonal signaling pathways [14, 15]. *Clostridium butyricum* CGMCC 0313.1

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(CB0313.1), a Gram-positive anaerobic bacillus naturally residing in the gut of humans and animals, has been shown to suppress lipogenesis through its bacterial wall components and metabolites, particularly butyrate [16]. Doumatey et al. [17] reported a strong association between gut microbiota and type 2 diabetes in urban Africans, suggesting its potential role in glycemic control. Hagihara et al. [18] pointed out that CB0313.1 modulates starch and sucrose metabolism in the intestine of mice, thereby enhancing carbohydrate metabolism. In a diabetic mouse model, and Jia et al. [19] confirmed the preventive and therapeutic effects of CB0313.1 on hyperglycemia and metabolic dysfunction.

Despite these promising findings, there is still limited research on the effects of CB0313.1 in schizophrenia patients with MS. This study aims to evaluate the therapeutic efficacy of CB0313.1 in improving MS in this population. Additionally, it explores changes in metabolic indicators, including BMI, blood sugar (BS), BP, and lipid profiles before and after CB0313.1 treatment, providing a clinical reference for the use of CB0313.1 in medication.

Patients and methods

Case selection

This retrospective study selected 100 schizophrenic patients with relatively stable conditions who were treated at The Third Hospital of Quzhou between January 2020 and December 2022. All patients continued their original antipsychotic drug treatment. Among them, 52 cases received additional CB0313.1 therapy were assigned to the observation group, while the remaining 48 cases, who did not receive CB0313.1, constituted the control group. The two groups showed clinical comparability, with no significant differences in baseline data.

Inclusion and exclusion criteria

Inclusion criteria: ① Age between 18 and 60 years; ② Diagnosis of schizophrenia according to *the International Classification of Diseases, 10th Revision (ICD-10): Classification of Mental and Behavioral Disorders - Diagnostic Criteria for Research* [20]; ③ Diagnosis of MS, defined as meeting three or more of the following criteria based on *the Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition)* [21]: a. Abdominal obesity (or central obesity): waist circumference (WC) ≥90 cm for males and ≥85 cm for females; b. Hyperglycemia: fasting blood glucose (FBG) ≥6.1 mmol/L or 2-hour post-load glucose ≥7.8 mmol/L, or prior diagnosis of diabetes with relevant treatment; c. Hypertension: BP ≥130/85 mm (1 mmHg =0.133 kPa) or a prior diagnosis of hypertension; d. Fasting triglyceride (TG) ≥1.70 mmol/L; e. Fasting high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L; ④ Clinically stable schizophrenia (no acute exacerbations for at least 3 months); ⑤ Stable antipsychotic medication regimen (no changes in drug type or dosage for at least 2 months); ⑥ Abnormal metabolic indicators: fasting insulin ≥15 μU/mL or homeostasis model assessment of insulin resistance (HOMA-IR) ≥2.5, and glycosylated hemoglobin (HbA1c) ≥5.7%; ⑦ Absence of extreme dietary modifications (e.g., ketogenic or very low-calorie diets) or intense physical activity during the preceding 3 months (to minimize confounding effects on metabolic data).

Exclusion criteria: ① Family history of obesity or previous history of endocrine diseases; ② Previous history of diabetes, MS, or other diseases affecting glucose-lipid metabolism; ③ Use of psychoactive drugs or history of substance abuse; ④ Diagnosis of severe mental illness, dementia or severe cognitive disorders per ICD-10 criteria; ⑤ Use of gastric motility drugs or weight loss drugs within the past month; ⑥ History of significant gastrointestinal disorders, such as active peptic ulcers, recurrent uncontrolled diarrhea, or gastrointestinal hemorrhage; ⑦ Pregnant or lactating women; ⑧ Presence of eating disorders; ⑨ Known history of severe drug allergies; ⑩ Secondary obesity, thyroid dysfunction, treatment-resistant schizophrenia, severe hepatic or renal insufficiency, autoimmune disease, or history of gastrointestinal surgery.

Intervention methods

CB0313.1 therapy: Patients in the observation group received *Clostridium butyricum* capsules (CGE Biopharmaceutical (Chongqing) Co., Ltd., S20040054). The medication was administered orally with warm water approximately half an hour after meals, 2 capsules per dose, 3 times daily.

Life-style intervention: The intervention was carried out mainly from the aspects of dietary control, physical exercise, and rehabilitation training. In terms of dietary control, patients

were instructed to follow a low-salt, low-fat or diabetic diet, with more intake of fruits and vegetables, and avoid alcohol consumption. As for physical exercise: patients were encouraged to engage in brisk walking for at least 20-40 minutes every day, depending on their physical tolerance, and progressively increased as appropriate. As to rehabilitation training, patients were encouraged to do table tennis, treadmill walking, and aerobic exercises for 30-60 minutes per session, 3-5 times a week, with intensity and duration adjusted based on individual tolerance.

Both the CB0313.1 therapy and lifestyle interventions were maintained continuously for 12 weeks.

Data collection

Obesity indices. BMI was calculated based on a patient's height and fasting body weight before and 12 weeks after intervention. Waist circumference (WC) was measured at 1 cm above the umbilicus with the patient in a supine position, at both time points.

BS indicators. Fasting cubital venous blood was collected before and 12 weeks after intervention. After centrifugation, serum levels of FBG and 2-hour postprandial blood glucose (2hPBG) were determined.

Blood lipid indices. Serum levels of TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and HDL-C were measured using an automatic biochemical analyzer (Skillsmodel Biotech (Beijing) Co., Ltd., Catalyst One).

BP parameters. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded before and 12 weeks after intervention.

Oxidative stress assessment. Serum levels of oxidative stress markers, including glutathione peroxidase (GSH-Px), total superoxide dismutase (T-SOD), and catalase (CAT) were measured using enzyme-linked immunosorbent assay (ELISA; Whenzhou KeMiao Biological Technology Co., Ltd., KMEHu011830, KMEHu014041, KM090384).

Assessment of the severity of schizophrenia symptoms. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of schizophrenia symptoms. This scale adopts a 7-point sale (1= none to 7= extremely severe), with higher score corresponding to more a severe condition. This scale included three subscales: the Positive Symptom Scale (7 items), the Negative Symptom Scale (7 items), and the General Psychopathology Scale (16 items).

Therapeutic efficacy evaluation. Treatment efficacy was assessed based on changes in PANSS scores, categorized as follows: markedly effective (score reduction rate >50%), effective (score reduction rate 20%-49%), and ineffective (score reduction rate <20%). The total effective rate was calculated as (markedly effective cases + effective cases)/total cases × 100%.

Quality of life assessment. The 36-item Short-Form Health Survey (SF-36) was used to evaluate patients' quality of life across three domains: physical function, psychological function, and social function. Each domain is scored from 0-100 with higher scores indicating better quality of life.

The primary outcomes included MS outcomes, obesity indices, BS indicators, blood lipid indices, BP parameters, PANSS scores, and therapeutic efficacy; whereas secondary outcomes included oxidative stress and SF-36 scores.

Statistical methods

Statistical analyses were performed using SPSS 22.0, and data visualization was conducted using Graphpad Prism 7.0. Categorical data were presented as counts (percentages), while continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Between-group comparisons were analyzed using the chi-square (χ^2) test or independent samples t-test, and within-group comparisons were conducted using the paired t-test. A *P*-value <0.05 was considered significant.

Results

Comparison of general information between the two groups

There were no significant differences between the observation and control groups in terms of sex, age, disease course, educational level, smoking history, or alcohol consumption history (P<0.05, **Table 1**).

Comparison of obesity indices between the two groups

No statistical inter-group difference was identified in BMI or WC before intervention (P>0.05).

Table 1. Comparison of baseline information between the two groups

Factor	Observation group (n=52)	Control group (n=48)	χ^2/t	P
Sex			0.289	0.591
Male	32 (61.54)	27 (56.25)		
Female	20 (38.46)	21 (43.75)		
Age (years)	45.85±9.54	45.19±10.82	0.324	0.747
Disease course (years)	5.42±1.99	4.67±2.05	1.856	0.067
Educational level			0.488	0.485
≤ Junior high school	14 (26.92)	16 (33.33)		
≥ Senior high school	38 (73.08)	32 (66.67)		
Smoking history			0.341	0.560
Yes	18 (34.62)	14 (29.17)		
No	34 (65.38)	34 (70.83)		
Alcoholism history			0.495	0.482
Yes	15 (28.85)	17 (35.42)		
No	37 (71.15)	31 (64.58)		

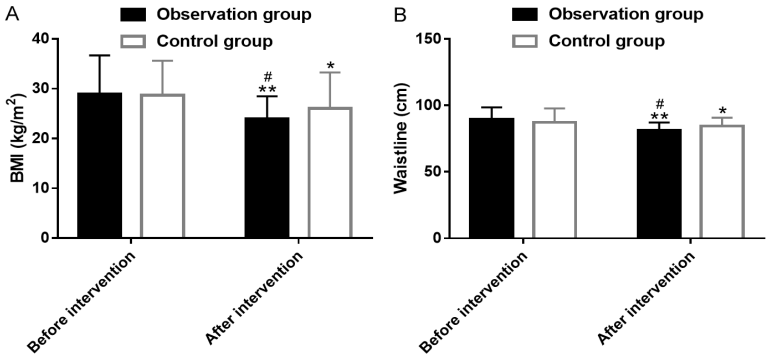

Figure 1. Comparison of obesity indices between the two groups before and after treatment. A. BMI: Body mass index; B. WC: Waist circumference. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

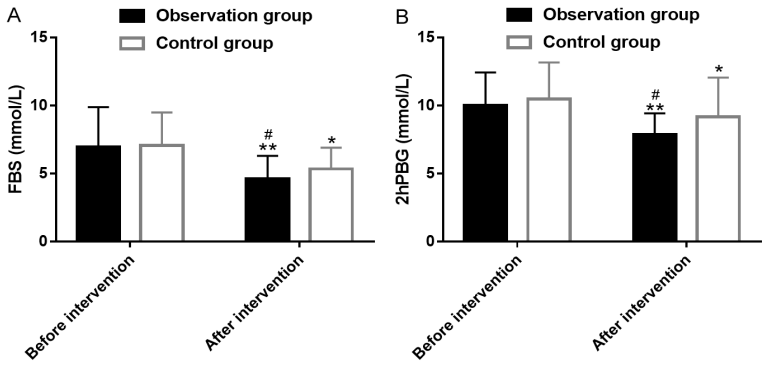

Figure 2. Comparison of blood glucose indicators between the two groups before and after the treatment. A. FBS: Fasting blood sugar; B. 2hPBG: 2-hour postprandial blood glucose. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

After 12 weeks of intervention, both groups showed significant reductions in these measures, with the observation group demonstrating significantly lower BMI and WC compared to the control group (P<0.05, **Figure 1**).

Comparison of blood sugar indicators between the two groups

FBG and 2hPBG were measured to assess blood sugar levels. There were no significant differences in FBS or 2hPBG between the two groups prior to the intervention (P>0.05). Post-intervention, both groups exhibited significant reductions in FBG and 2hPBG (P<0.05), with the observation group achieving significantly lower FBS and 2hPBG levels than the control group (P<0.05, **Figure 2**).

Comparison of lipid profiles between the two groups

Serum levels of TG, TC, LDL-C, and HDL-C were assessed to evaluate lipid metabolism. Before intervention, no significant differences were identified between the two groups (P>0.05). After intervention, both groups showed significant decreases in TG, TC, and

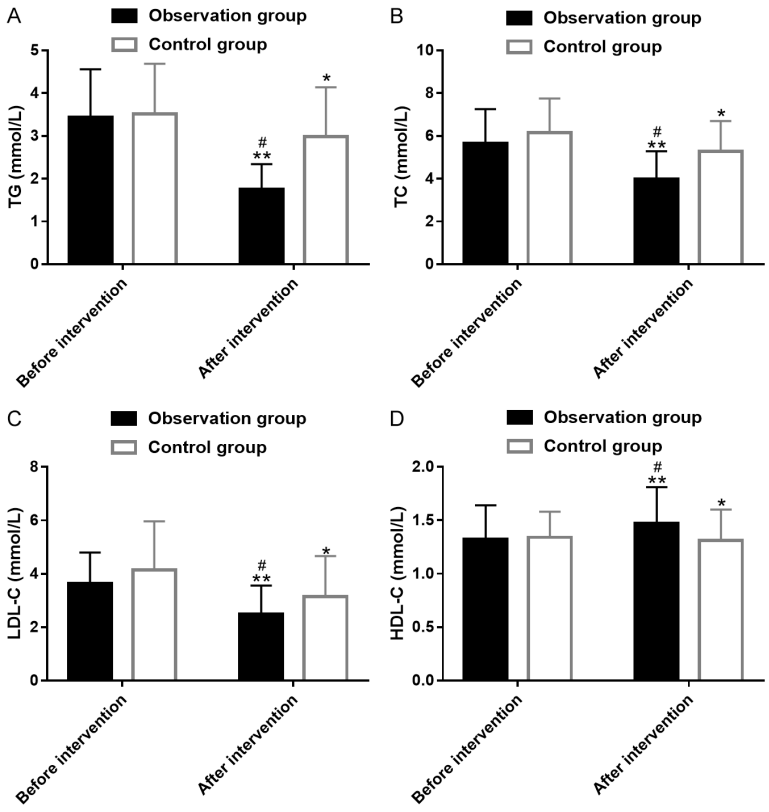

Figure 3. Comparison of lipid profiles between the two groups before and after the treatment. A. TG: Triglyceride; B. TC: Total cholesterol; C. LDL-C: Low-density lipoprotein cholesterol; D. HDL-C: High-density lipoprotein cholesterol. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

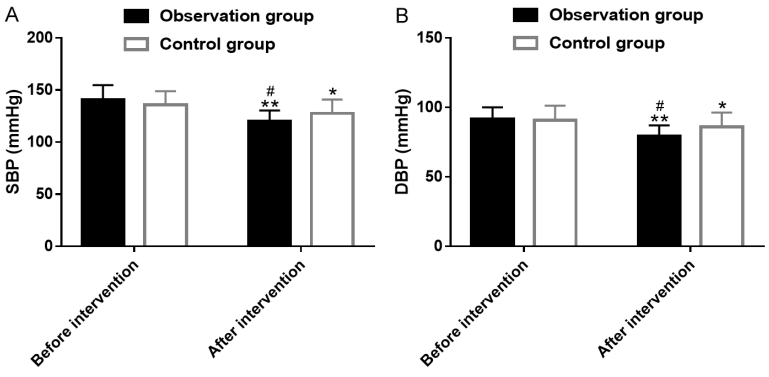

Figure 4. Comparison of blood pressure between the two groups before and after the treatment. A. SBP: Systolic blood pressure; B. DBP: Diastolic blood pressure. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

LDL-C, along with increases in HDL-C (P<0.05). Notably, significantly lower TG, TC, and LDL-C levels and higher HDL-C levels were determined in the observation group compared to the control gorup (P<0.05, **Figure 3**).

Comparison of blood pressure between groups

SBP and DBP were recorded before and after the intervention. Baseline SBP and DBP values were similar between the two groups (P>0.05). Post-intervention, both groups showed significant reductions in SBP and DBP (P<0.05), with the observation group achieving significantly lower values than the control group (P<0.05, **Figure 4**).

Comparison of oxidative stress indicators between groups

Oxidative stress levels were assessed by measuring serum levels of GSH-Px, T-SOD, and CAT. At baseline, no significant differences were observed in these markers between the two groups (P>0.05). After 12 weeks of intervention, both groups exhibited significant increases in GSH-Px and T-SOD levels, accompanied by a significant decrease in CAT levels (P<0.05). Notably, the observation group demonstrated significantly higher GSH-Px and T-SOD levels, as well as significantly lower CAT levels, compared to the control group (P<0.05). The details are shown in **Figure 5**.

Comparison of severity of schizophrenia symptoms between the two groups

The severity of schizophrenia was assessed using the PANSS, including the positive symptom subscale, negative symptom subscale, and general psychopathology subscale. Baseline scores for all three subscales didn't differ significantly between the two groups (P>0.05). After the intervention, all scores decreased in both groups (P<0.05). No-

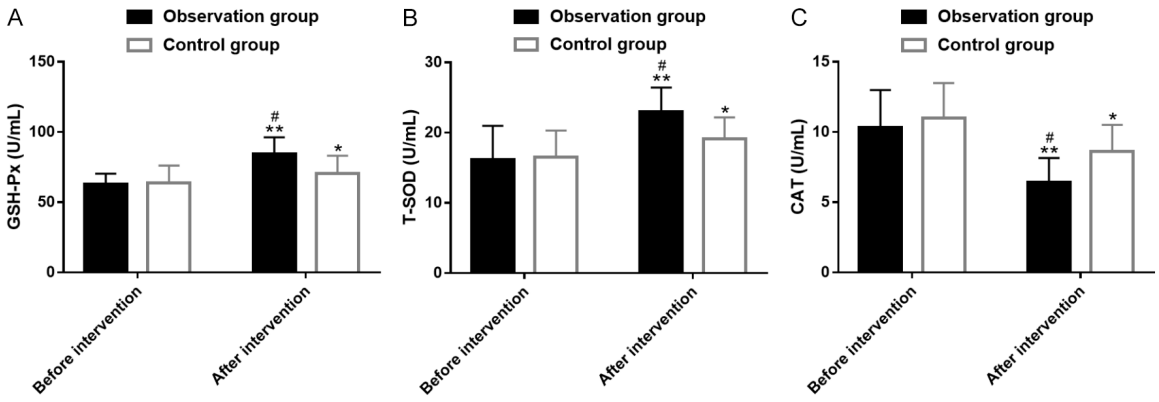

Figure 5. Comparison of oxidative stress indicators between the two groups before and after the treatment. A. GSH-Px: Glutathione peroxidase; B. T-SOD: Total superoxide dismutase; C. CAT: Catalase. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

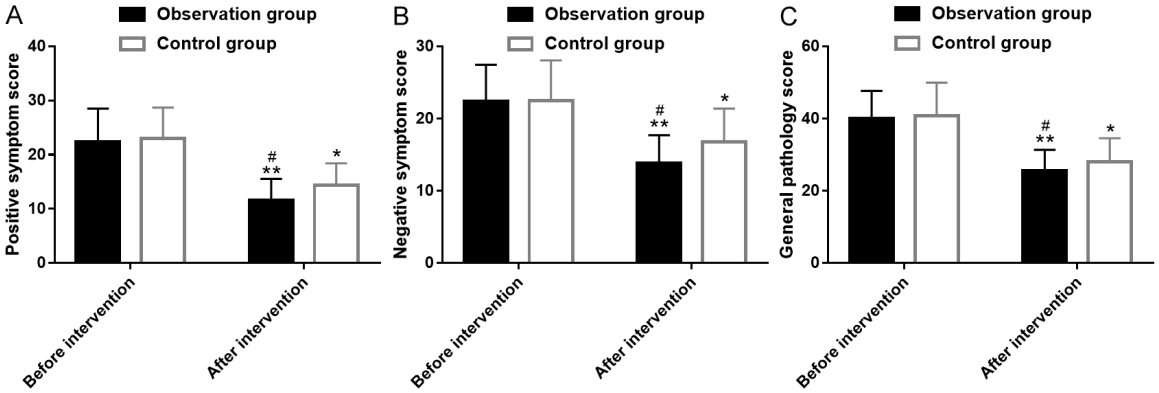

Figure 6. Comparison of schizophrenia severity between the two groups before and after the treatment. A. Positive symptom scores; B. Negative symptom scores; C. General psychopathology scores. Note: *P<0.05, **P<0.01 vs. before intervention; #P<0.05 vs. control group.

tably, the levels of all these indicators in the observation group were discernibly lower than those of the control group (P<0.05, **Figure 6**).

Therapeutic efficacy

A statistically significant difference was observed in overall treatment efficacy between the two groups. Specifically, a notably higher total effective rate was determined in the observation group compared to the control group (P<0.05, **Table 2**).

Quality of life

Patients' quality of life was assessed using the SF-36 scale before and after intervention focusing on physical, psychological, and social functioning. At baseline, no significant differences were observed between the two groups across all three domains (P>0.05). After the 12-week intervention, both groups exhibited significant improvements in all three domains (P<0.05). However, no significant disparities were noted between the two groups in any of the three domains (P>0.05), as shown in **Figure 7**.

Discussion

Schizophrenia, one of the top ten causes of disability worldwide, affects nearly 1% of the world's population [22]. Although antipsychotic medications remain the cornerstone of schizophrenia treatment, they are associated elevated risk of developing MS, with reported prevalence ranging from 37% to 63% [23]. This study proposes a therapeutic regimen from the perspective of gut microbiota modulation, which may help address the above problems.

Previous studies on CB0313.1 therapy have primarily focused on its neuroprotective effects,

Table 2. Comparison of therapeutic efficacy between the two groups

Efficacy	Observation group (n=52)	Control group (n=48)	χ^2	P
Markedly effective	21 (40.38)	14 (29.17)		
Effective	26 (50.00)	22 (45.83)		
Ineffective	5 (9.62)	12 (25.00)		
Total efficacy	47 (90.38)	36 (75.00)	4.187	0.041

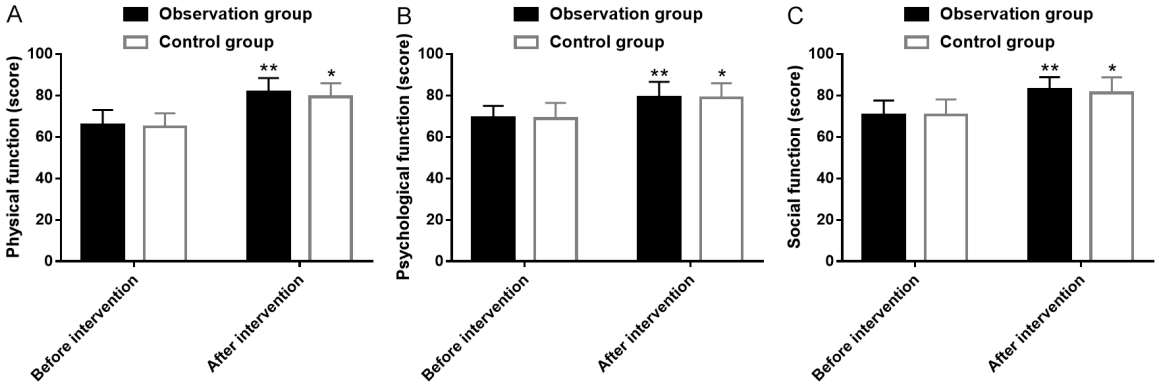

Figure 7. Comparison of patient's quality of life between the two groups before and after the treatment. A. Physical function; B. Psychological function; C. Social function. Note: *P<0.05, **P<0.01 vs. before intervention.

with limited data on its clinical efficacy in schizophrenia complicated by MS [24]. For example, Liu et al. [25] demonstrated that CB0313.1 exerted neuroprotective effects in a mouse model of vascular dementia by regulating brain-derived neurotrophic factor (BDNF)-phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway-associated proteins and gut microbiota. Similarly, Sun et al. [26] found that CB0313.1 alleviated depressive-like behaviors induced by chronic unpredictable mild stress, possibly through regulating the levels of gut-brain axis-associated mediators. In this study, the clinical efficacy of CB0313.1 in patients with schizophrenia complicated with MS was compared with those undergoing lifestyle interventions alone. Obesity was evaluated by BMI and WC. The observation group exhibited notably reduced BMI and WC after intervention compared to the control group, demonstrating a more pronounced anti-obesity effect of CB0313.1. This aligns with the findings of Liao et al. [27], who proposed that the anti-obesity mechanisms of CB0313.1 may be mediated through modulation of gut microbial composition and gut-derived metabolites, independent of butyrate production, thereby shifting metabolic phenotypes under a high-fat dietary conditions. The above findings demonstrated that CB0313.1 exerts favorable effects on obesity-related data in schizophrenia patients with comorbid MS, outperforming lifestyle interventions alone.

In terms of blood sugar regulation, FBS and 2hPBG were markedly reduced in the observation group after intervention, with values markedly lower than both baseline and the control group. Previous studies have shown that CB-0313.1 exerts a comparable preventive effect on diabetes to metronidazole in treating *clostridium difficile* infections, indicating its potential role in blood glucose regulation [28]. Regarding lipid metabolism, serum levels of TG, TC, and LDL-C notably reduced after intervention in the observation group, while HDL-C significantly elevated. All post-treatment values were significantly more favorable than both baseline and the control group, indicating that CB0313.1 treatment was more effective than lifestyle intervention in improving lipid profiles in schizophrenia patients with MS. Similarly, Long et al. [29] reported that CB0313.1 alleviated lipid abnormalities in mice by enhancing gut health and reducing serum lipid levels.

Further, SBP and DBP were significantly reduced in the observation group compared to baseline and the control group after intervention, suggesting a beneficial effect of CB0313.1

on blood pressure regulation. CB0313.1 is shown to relieve high-fat diet-induced intestinal inflammation and hypertension by promoting the secretion of short-chain fatty acid, thereby supporting its anti-obesity and anti-hypertension effects [30, 31]. These findings collectively indicate that CB0313.1 has an effective and positive regulatory effect on metabolic disorders in schizophrenic patients with MS. This may be attributed to its ability to stimulate intestinal hormone secretion, relieve constipation, and modulate gut microbiota composition, thereby restoring microbial balance [32, 33].

Additionally, CB0313.1 significantly attenuated oxidative stress, as evidenced by its superior efficacy over lifestyle interventions in upregulating GSH-Px and T-SOD levels while downregulating CAT levels. Alleviation of oxidative stress has been shown to reduce MS risk and partially inhibit inflammatory responses in schizophrenic [34]. GSH-Px, a key peroxidase enzyme, correlates positively with psychiatric symptom severity and interleukin (IL)-6 levels. T-SOD, an oxidative factor, enhances systemic antioxidant capacity, while elevated CAT levels indicate impaired hydrogen peroxide clearance. These biomarkers are central to the pathophysiologic process of schizophrenia [35, 36].

CB0313.1 also significantly alleviated the severity of schizophrenia symptoms and improved overall therapeutic efficacy compared to lifestyle intervention. Furthermore, CB0313.1 remarkably improved patients' quality of life although the improvement was not statistically significant when compared to the control groups. In summary, CB0313.1 treatment contributes to better glycemic control, lipid metabolism, and BP management, and reduced oxidative stress, while simultaneously alleviating psychiatric symptoms and enhancing treatment outcomes and quality of life in patients with schizophrenia and comorbid MS.

This study has several limitations. First, the relatively small sample size (n=100) and short intervention period (12 weeks) may limit the generalizability of the findings. Future studies with larger, multicenter cohorts and extended follow-up durations (e.g., 6 to 12 months) are warranted to validate the long-term efficacy and safety of CB0313.1. Second, as all participants continued their baseline antipsychotic regimens (e.g., olanzapine, risperidone), potential variations in metabolic effects across different antipsychotics were not assessed. Additional stratified analyses by medication type are needed to clarify potential drug-drug interactions with CB0313.1. Third, the study lacked mechanistic investigations, particularly regarding gut microbiota modulation. Incorporating multi-omics approaches, such as metagenomics and metabolomics, in future research may help elucidate the underlying mechanisms of CB0313.1's therapeutic effects.

Our results all indicate that CB0313.1 is effective in improving clinical outcomes in schizophrenic patients with MS. CB0313.1 significantly enhances metabolic parameters, including body weight, blood glucose, lipid profile, and blood pressure, while also improving oxidative stress markers, alleviating psychiatric symptom severity, and enhancing overall therapeutic efficacy and quality of life. CB0313.1 represents a promising adjunctive treatment strategy for managing schizophrenia complicated by metabolic syndrome.

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Disclosure of conflict of interest

None.

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