Journal of Affective Disorders 295 (2021) 163–172

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Clozapine induces metformin-resistant prediabetes/diabetes that is associated with poor clinical efficacy in patients with early treatment-resistant schizophrenia

Chuanjun Zhuo [g,1,*], Yong Xu [e,1], Haibo Wang [f,1], Chuanhua Zhou [g], Jian Liu [h], Xiaocui Yu [b,c,h], Hailin Shao [a,b,c], Hongjun Tian [a,b,c], Tao Fang [a,b,c], Qianchen Li [g], Jiayue Chen [d,b,c], Shuli Xu [b,c,d], Xiaoyan Ma [b,c,d], Weiliang Yang [b,c,d], Cong Yao [b,c,d], Bo Li [b,c,i], Anqu Yang [b,c,i], Yuhui Chen [b,c,i], Gongyong Huang [j,*], Chongguang Lin [j,*]

[a] *Key Laboratory of Multiple Organ Damages of Major Psychoses (MODMP_Lab), Tianjin fourth center Hospital, Tianjin Medical Affiliated Tianjin Fourth Central Hospital, Nankai University Affiliated Tianjin Fourth Center Hospital, Tianjin 300140, China*
[b] *National Center of Endocrine and Metabolic Disease Comprehensive Management(MMC), Tianjin fourth center Hospital, Tianjin Medical Affiliated Tianjin Fourth Central Hospital, Nankai University Affiliated Tianjin Fourth Center Hospital, Tianjin 300140, China*
[c] *Key laboratory of Real Time Brain Circuits Tracing of Neurology and Psychiatry (RTBNB_Lab), Tianjin fourth center Hospital, Tianjin Medical Affiliated Tianjin Fourth Central Hospital, Nankai University Affiliated Tianjin Fourth Center Hospital, Tianjin 300140, China*
[d] *Key Laboratory of Psychiatry Neuroimaging-genetics and Co-morbidity (PNGC_Lab), Tianjin Medical University Clinical Hospital of Mental Health, Tianjin Anding Hospital, Nankai University Affiliated Tianjin Anding Hospital, Tianjin Mental Health Center, Tianjin 300222, China*
[e] *Department of Psychiatry, First Clinical Medical College, First Hospital of Shanxi Medical University, Taiyuan 030000, China*
[f] *Peking University Clinical Research Institute, Peking University First Hospital, Beijing, 100191, China*
[g] *Department of Pharmacoloy, The First Hospital of Hebei Medical University, Shijiazhuang 05000, Hebei Province, China*
[h] *Clinical Laboratory, Tianjin Medical University Clinical Hospital of Mental Health, Tianjin Anding Hospital, Nankai University Affiliated Tianjin Anding Hospital, Tianjin Mental Health Center, Tianjin 300222, China*
[i] *Department of Psychiatry, Tianjin Kangtai Mental Health Hospital, Tianjin 300014, China*
[j] *Department of Psychiatry, Wenzhou Seventh Peoples Hospital, 325000, China*

ARTICLE INFO

Keywords:
Schizophrenia
Treatment-resistant schizophrenia
Prediabetes
Diabetes
Clozapine
Metformin

ABSTRACT

Background: Two distinct subtypes of treatment-resistant schizophrenia (TRS) have been recently reported, including early-treatment resistance (E-TR) and late-treatment resistance (L-TR). This study was to assess clozapine-induced metformin-resistant prediabetes/diabetes and its correlation with clinical efficacy in schizophrenia E-TR subtype.

Methods: This prospective cohort study enrolled 230 patients with schizophrenia E-TR subtype and they were treated with adequate doses of clozapine for 16 weeks, during which patients with prediabetes/diabetes were assigned to receive add-on metformin. The main outcomes and measures included incidence of clozapine-induced prediabetes/diabetes and metformin-resistant prediabetes/diabetes, and the efficacy of clozapine as assessed by the Positive and Negative Syndrome Scale (PANSS) score.

Results: Clozapine-induced prediabetes/diabetes occurred in 76.52% of patients (170 prediabetes and 6 diabetes), of which the blood sugar of 43 (24.43%) patients was controlled with metformin. Despite add-on metformin, 47.06% (74/170) of prediabetes patients progressed to diabetes. In total, the incidence of clozapine-induced metformin-resistant prediabetes/diabetes was 75.57% (133/176). On completion of 16-week clozapine treatment, 16.52% (38/230) patients showed clinical improvement with PANSS scores of ≥50% declining. Furthermore, clozapine-induced prediabetes/diabetes was significantly correlated with the poor clinical efficacy of clozapine for schizophrenia E-TR subtype.

Abbreviation: TRS, treatment-resistant schizophrenia; E-TR, early-treatment resistance; L-TR, late-treatment resistance; OGTT, oral Glucose Tolerance Test; FBG, fasting blood glucose; PPG, postprandial glucose; PANSS, Positive and negative symptoms scale; TESS, Treatment Emergent Symptom Scale; SD, standard deviation; ANOVA, analysis of variance; ECT, electroconvulsive therapy; LOCF, last observation carried forward.

* Corresponding authors.
E-mail addresses: chuanjunzhuotjmh@163.com, chuanjunzhuo@nandkai.edu.cn (C. Lin).
[1] These authors contributed equally to this work and should be considered as co-first authors.

https://doi.org/10.1016/j.jad.2021.08.023
Received 24 July 2021; Received in revised form 10 August 2021; Accepted 18 August 2021
Available online 23 August 2021
0165-0327/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Conclusions: The incidence of clozapine-induced metformin-resistant prediabetes/diabetes was considerably high in the schizophrenia E-TR subtype. Clozapine-induced metformin-resistant prediabetes/diabetes represents an independent risk factor that adversely affects the clinical efficacy of clozapine for the schizophrenia E-TR subtype. This study provided new evidence for re-evaluating the use of clozapine for TRS, especially E-TR subtype, and the use of metformin for the glycemic control of clozapine-induced prediabetes/diabetes.

1. Introduction

Treatment-resistant schizophrenia (TRS) represents a major challenge to mental health care, impacting approximately 30% of schizophrenia patients. Two distinct subtypes of TRS have been identified: "early-treatment resistance" (E-TR) and "late-treatment resistance" (L-TR) (Lally et al., 2016; Mena et al., 2018; Rachamallu et al., 2017; Westfall et al., 2018). Of note, most patients with schizophrenia fall in the E-TR subtype (Lally et al., 2016; Mena et al., 2018). Previous studies reported that schizophrenia patients with the E-TR subtype have different biological bases and poorer prognosis in comparison to patients with the L-TR subtype (Lally et al., 2016; Mena et al., 2018; Rachamallu et al., 2017; Westfall et al., 2018; Robinson et al., 1999). To date, studies on these two subtypes of schizophrenia remain limited.

Clozapine is currently the only evidence-based psychotic that is approved for patients with TRS, despite controversy over metabolic adverse events (e.g., prediabetes and diabetes) (Samara et al.,2016; Leucht et al., 2013; Wells and McCormack 2020; Balcioglu et al., 2020; Stokes et al., 2020). In fact, switching to the clozapine strategy is highly recommended to treat patients with TRS (Wells and McCormack 2020; Barnes et al., 2020; Keepers et al., 2020). However, few studies have evaluated the efficacy of clozapine and incidence of clozapine-induced prediabetes/diabetes in schizophrenia E-TR subtype. Considering the high-risk of clozapine for metabolic syndrome in schizophrenia (Addington et al., 2017; Flanagan et al., 2020; Borrelli et al.,2020), it is important to assess the risks and benefits of switching to clozapine for treating patients with schizophrenia E-TR subtype.

Clozapine has various side effects, of which metabolic syndrome (e.g., hyperglycemia, hyperlipidemia hypertension, weight gain) is associated with an increased risk of cardiovascular disease and subsequent mortality of patients with schizophrenia (Siskind et al., 2020; Zhou et al., 2021; Sun and Jang 2020). Previous studies have also indicated that clozapine-induced prediabetes and diabetes contribute to the increased risk of mortality in schizophrenic patients (Siskind et al., 2020; Lappin et al., 2018; Siskind et al., 2018; Liu et al., 2017; Zimbron et al., 2016; Hyde et al., 2015). The prevalence of antipsychotic-induced diabetes/prediabetes was as high as 22.3% in Chinese patients with schizophrenia, and the odds ratio (OR) was 4.37 compared to individuals without schizophrenia (Mitchell et al., 2013; Zhang et al., 2011). Antipsychotics cause the risk of developing diabetes to rise 3.6-fold in schizophrenic patients taking antipsychotics in comparison to control individuals (Huo et al., 2021; Andreassen 2017). Larsen and colleagues reported that the prevalence of prediabetes in overweight or obese schizophrenic patients treated with clozapine or olanzapine was as high as 69.7% (Andreassen 2017; Rajkumar et al., 2017; Larsen et al., 2018). These findings have undermined the clinical importance and urgent need for the effective management of prediabetes/diabetes in schizophrenic patients (Manu et al., 2012; Cernea et al., 2020; Svensson et al., 2019; Larsen et al., 2017). However, few studies have reported the incidence of clozapine-induced prediabetes/diabetes in patients with schizophrenia E-TR subtype.

Metformin has been extensively used as a cost-effective medication to control high blood sugar in diabetes, exhibiting potential beneficial properties (e.g., lower risk of fatal cardiovascular events related to diabetes); however, the use of metformin in preventing prediabetes is subject to controversy (Cernea et al., 2020; Warrilow et al., 2020; Clemmensen et al., 2021; de Boer et al., 2021; Wu et al., 2006; Grajales et al., 2019). Metformin also alleviates antipsychotic-induced hyperglycemia and hyperlipidemia (Jiang et al., 2020; Correll et al., 2020; Stroup and Gray 2018; de Boer et al., 2021). These studies indicate that metformin alleviates antipsychotics-induced prediabetes/diabetes and associated comorbidities in patients with schizophrenia (Stroup and Gray 2018; de Boer et al., 2021; Wu et al., 2006). However, few studies have reported the effects of metformin at preventing clozapine-induced prediabetes/diabetes and the clinical efficacy of clozapine in patients with schizophrenia E-TR subtype. More awfully, there has been mounting evidence that antipsychotic agents, especially clozapine and olanzapine, induced prediabetes/diabetes/ metabolic syndrome, can conversely reduce the therapeutic effect of these antipsychotic agents (Cernea et al., 2020; Grajales et al., 2019; Pillinger et al., 2017). Based on the above-mentioned findings, the relationship between clozapine-induced prediabetes/diabetes and efficacy of clozapine is complex. As such, further insight into the complicated relationship is urgent needed, and the new findings may provide better management that promotes prevention and care for such patients in the next years (Masuda et al., 2019).

Here, we evaluated the incidence of clozapine-induced prediabetes/diabetes in a cohort of patients with schizophrenia E-TR subtype. In parallel, we investigated the effects of metformin on clozapine-induced prediabetes/diabetes, efficacy of clozapine treatment, and the relationship between the clozapine-induced prediabetes/diabetes and the clinical efficacy. The findings obtained through conducting this study were anticipated to offer new evidence on preventive interventions for clozapine-induced prediabetes/diabetes in patients with schizophrenia E-TR subtype.

2. Materials and methods

2.1. Participants

For this cohort study, 230 patients with schizophrenia E-TR subtype were recruited from Tianjin Kangtai Hospital (Tianjin, China) between January 2015 and December 2020. The inclusion and exclusion criteria during patient enrollment are presented in the Supplementary Material.

Signed written informed consent was acquired from all participants and their guardians. The study protocol was reviewed and approved by the Ethic Committee of Tianjin Kangtai Hospital (Tianjin, China). This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation.

2.2. Interventions

Two-hundred and thirty patients with schizophrenia E-TR subtype were treated with clozapine according to the Chinese Psychiatric Association guideline for treating patients with schizophrenia. Fasting blood glucose (FBG) and postprandial glucose (PPG) were monitored weekly, while blood lipids, liver function, kidney function, PLT, and WHR were examined every four weeks. Based on World Health Organization guidelines for diagnosing and classifying diabetes, prediabetes was defined as impaired fasting glucose (fasting plasma glucose, 6.1-6.9 mmol/L) or 2-h PPG using the Oral Glucose Tolerance Test (OGTT) (7.8-11 mmol/L), while type 2 diabetes was defined as a fasting plasma glucose >7.1 mmol/L or 2-h PPG at OGTT>11 mmol/L) (Somannavar et al., 2009). Hyperlipidemia/hypercholesterolemia was defined as triglyceride >1.7 mmol/L and cholesterol >5.7 mmol/L.

Hyperprolactinemia was defined as PLT >80 μg/L. Abdominal obesity was defined as WHR >0.9 for males, and >0.85 for females. During 2-4 weeks period of titrating clozapine, diazepam (5-30mg/per day) was given to the patients as a replacement according to the patients' tolerance. If the patients had serious side effects, the dosage was decreased to the appropriate dosage or the medication was terminated. The dosage range of the clozapine was 200~900mg/day (We acquired the signed informed consent for overdose medication from the patients or their guardians.

When clozapine-induced prediabetes occurred, affected patients were given metformin with meals. Metformin was given as an intervention strategy, with a daily dose of 1.0 g (Copeland et al., 2010), and the patient was monitored for any effects of metformin. If diabetes progressed from clozapine-induced prediabetes, or hyperlipidemia/hypercholesterolemia developed, affected patients were reviewed by an expert endocrinologist in the Department of Endocrinology, Tianjin Kangtai Hospital. If patients had hyperprolactinemia, traditional Chinese medicines were used to alleviate the condition, during which other antipsychotic agents (e.g., Aripiprazole) were not used, to avoid any potential influence on this study.

All 230 patients received regular clozapine treatment for 16 weeks at adequate doses. The Positive and negative symptoms scale (PANSS) and Treatment Emergent Symptom Scale (TESS) were used to evaluate any adverse reactions to drugs. Over the entire period of the study, the blood concentration of clozapine was monitored weekly to ensure adequate therapeutic concentrations were maintained.

2.3. Outcome measures

Primary outcome measures included: (1) incidence of clozapine-induced prediabetes/diabetes in schizophrenia E-TR subtype patients; (2) effect of metformin on clozapine-induced-prediabetes/diabetes in schizophrenia E-TR subtype patients; (3) efficacy of clozapine in the treatment of schizophrenia patients with E-TR subtype. using PANSS; (4) correlation between the clinical efficacy of clozapine and clozapine-induced prediabetes/diabetes when treating schizophrenia patients with E-TR subtype. For the PANSS scores, improvement in treatment was defined as a ≥50% reduction in the total PANSS score following 16 weeks of treatment; partial-improvement was defined as a ≥30% to <50% reduction, and no improvement was defined as a <30% reduction.

Secondary outcomes included: (1) risk factors influencing the clinical efficacy of clozapine; (2) risk factors associated with clozapine-induced prediabetes/diabetes; and (3) the incidence and categories of adverse clozapine-induced events in treating schizophrenia E-TR subtype patients.

2.4. Statistical analysis

Statistical analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA). Normally distributed data were expressed as mean ± standard deviation (SD), while continuous variables were expressed as median ± interquartile range for non-normal data. Categorical variables were presented as numbers and percentages. The difference between the four prediabetes/diabetes subgroups on demographic characteristics, clinical characteristics, and total clozapine dosage over the 16-week period were compared using analysis of variance (ANOVA) (or Kruskal-Wallis rank sum test) and chi-square test/Fisher's exact test, as appropriate. Homogeneity of variance was evaluated for ANOVA using Levene's test. Greenhouse-Geisser correction was applied when the sphericity assumption was not met. To correct for missing values, the last observation carried forward (LOCF) method was used for the last follow-up data at week 16, due to poor treatment responses and transferal to other hospitals. Among the participants treated with clozapine, univariate and multivariate associations of clinical-demographic characteristics with an improvement of blood glucose level were evaluated with a logistic regression model and expressed as odds ratios (ORs) with 95% confidence interval (CIs).

3. Results

3.1. Study population

A total of 230 patients with schizophrenia E-TR subtype who met the eligibility criteria were enrolled in this study (Suppl. Fig. 1). The demographic characteristics and clinical features of the study subjects are summarized in Table 1 and Suppl. Tables 1 & 2. The study patients were classified into four groups according to whether prediabetes/diabetes occurred during clozapine treatment over the 16-week study period: Group A, no occurring clozapine-induced prediabetes/diabetes (n = 54, 23.5%); Group B, clozapine-induced prediabetes with abnormally high blood sugar controlled by metformin (n = 43, 18.7%); Group C, clozapine-induced prediabetes with abnormally high blood sugar not controlled by metformin, with no progression to diabetes (n = 53, 23.0%); and group D, clozapine-induced prediabetes or diabetes with abnormally high blood sugar not controlled by metformin, and with prediabetes progressing to diabetes (n = 80, 34.8%). The study subjects in the four groups exhibited no significant differences in demographic or other characteristics (Table 1).

3.2. Incidence and risk factors of clozapine-induced prediabetes/diabetes

During the 16-week period of clozapine treatment, 176 patients developed prediabetes/diabetes, with a 76.52% incidence of clozapine-induced prediabetes/diabetes. Specially, 170 patients (73.91%) had clozapine-induced prediabetes, while six patients (2.61%) directly developed diabetes without progressing from prediabetes. Of the 170 patients with clozapine-induced prediabetes, 74 patients (47.06%) progressed to full diabetes. Multivariate analysis showed that illness duration before clozapine treatment, FBG at baseline, PLT at baseline, and family history of diabetes represented risk factors of clozapine-induced prediabetes (Suppl. Table 3).

3.3. Effect of metformin on the prevention and progression of clozapine-induced prediabetes to full diabetes

We examined the effect of daily metformin administration at a dose of 1.0 g on the prevention and progression of clozapine-induced prediabetes to full diabetes. Unexpectedly, a considerably high proportion of patients [75.57% (74 in Group D, 53 in Group C, and 6 in Group D) out of 176 patients] developed prediabetes/diabetes. In contrast, 24.43% of patients (43/176) had abnormally high blood sugar that was controlled by metformin treatment. In this cohort study, clozapine-induced prediabetes/diabetes not controlled by metformin was defined as metformin resistant prediabetes and metformin resistant diabetes. Overall, 127 patients had metformin resistant clozapine-induced prediabetes, with 74.70% occurrence rates [74+53)/170]. A further six (2.61%) patients had metformin resistant clozapine-induced diabetes. Unfortunately, the efficiency of metformin in preventing clozapine-induced diabetes was 0% (0/6 patients).

3.4. Clinical efficacy of clozapine and correlation with clozapine-induced prediabetes/diabetes in treating schizophrenia E-TR subtype

Assessment of the clinical efficacy of clozapine treatment showed that 16.52% (38/230) patients clinically improved based on the PANSS score. The PANSS score reduced ≥50% by the end of the 16-week clozapine treatment. In contrast, 70.87% (163/230) patients exhibited no clinical improvement after switching to clozapine, with the PANSS score reducing <30%. The remaining 12.61% (29/230) patients showed partial improvement after completing the 16-week clozapine treatment, with the PANSS score reducing by 30%~50%. Further comparative

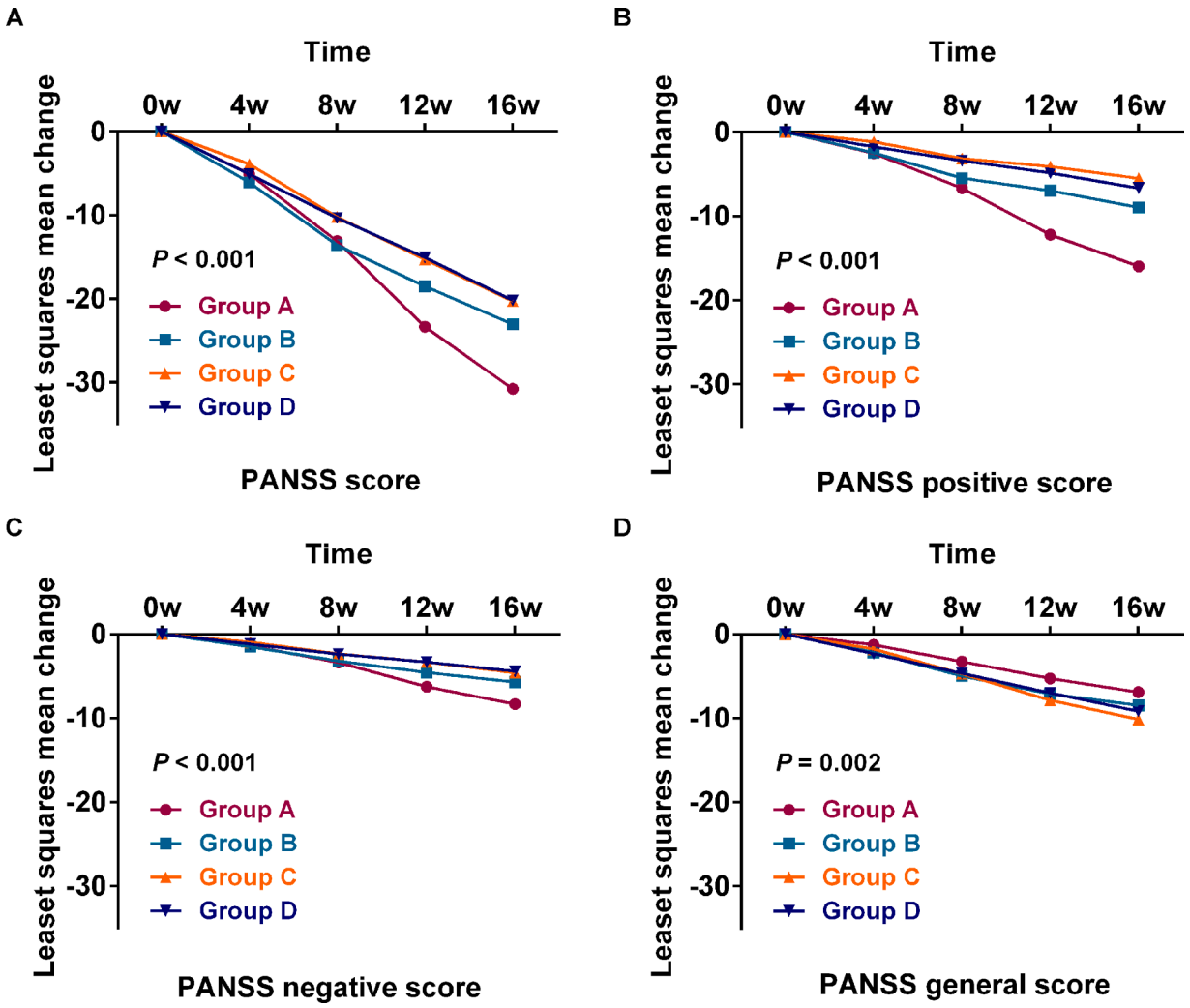


Fig. 1. Least squares means for groups at baseline and after 16 weeks of treatment. (A) PANSS total score; (B) PANSS positive score; (C) PANSS negative score; and (D) PANSS general score at baseline and after 16 weeks of treatment in the prediabetes/diabetes subgroups. Least-squares mean change was adjusted for age, sex, family history of diabetes, occurrence of waist hip ratio fat, occurrence of hypertriglyceridemia, occurrence of hypercholesterolemia, with prolactin >80 ug/l during treatment, and total dose of clozapine at 16 weeks. P value was calculated for group × time interaction with repeated-measures analysis of variance, adjusting age, sex, family history of diabetes, occurrence of waist hip ratio fat, occurrence of hypertriglyceridemia, occurrence of hypercholesterolemia, with prolactin >80 ug/l during treatment, and total dose of clozapine at 16 weeks. Group A, no occurring clozapine-induced prediabetes/diabetes; Group B, occurring clozapine-induced prediabetes with their abnormally high blood sugar under control by metformin; Group C, occurring clozapine-induced prediabetes with their abnormally high blood sugar not controlled by metformin, but without progression to diabetes; and group D, occurring clozapine-induced prediabetes or diabetes with abnormally high blood sugar not controlled by metformin, and with prediabetes progressing into diabetes.
LOCF, last observation carried forward.

analysis of the clinical efficacy of clozapine treatment showed a significant difference among the four groups. In particular, the highest clinical efficacy was observed in Group A, followed by group B, C, and D (Fig. 1).

Forty-four (19.13%) patients were administrated with clozapine-augmented electroconvulsive therapy (ECT) treatment, due to severe suicidal ideation/attempts and clozapine-related obsessive-compulsive symptoms. Thirteen (29.55%, 13/44) patients showed a significant reduction in the severity of suicidal ideation/attempts after receiving 6-12 ECT augmentation treatments, with no clinical improvement in 26 (59.1%, 26/44) patients. For five patients (13.6%, 5/44) with clozapine-induced obsessive-compulsive symptoms, we reduced the dosage of clozapine to alleviate symptoms, and added ECT to improve psychotic symptoms. After ECT treatments, only two patients showed any alleviation of psychotic symptoms. Three patients had unrelieved psychotic symptoms; although, clozapine-induced obsessive-compulsive symptoms were resolved after reducing the dosage of clozapine.

Univariate and multivariate logistic regression analyses showed that clozapine-induced prediabetes was an independent risk factor that was significantly associated with reduced clinical efficacy (Table 2 and Suppl. Table 4). In addition, family history of diabetes and hypertriglyceridemia were identified as independent risk factors leading to a reduced clinical efficacy of clozapine treatment (Table 2). Clozapine-induced prediabetes/diabetes was significantly correlated with reduced efficacy of clozapine, regardless of whether metformin controlled high blood sugar. Of note, the lowest clinical efficacy was observed in patients with clozapine-induced prediabetes that had high blood sugar not controlled by metformin, with this condition progressing to full diabetes (Tables 2 & 3). Although high blood sugar was under control in patients with clozapine-induced prediabetes and the condition did not progress to full diabetes, the efficacy of clozapine was significantly lower in these patients compared those that did not have clozapine-induced prediabetes (Tables 2 & 3).

Table 1.
Baseline characteristics and biochemical assessment in patients with schizophrenia E-TR subtype by prediabetes/diabetes subgroup.

		Group A (N=54)	Group B (N=43)	Group C (N=53)	Group D (N=80)	*P* value
Sex	Male	30 (55.6)	28 (65.1)	30 (56.6)	47 (58.8)	0.79
	Female	24 (44.4)	15 (34.9)	23 (43.4)	33 (41.3)	
Age		23.00 ± 1.80	23.23±1.57	23.17±1.48	23.31±1.50	0.73
Education level (Years)	≤12	9 (16.7)	4 (9.3)	5 (9.4)	8 (10.0)	0.56
	>12	45 (83.3)	39 (90.7)	48 (90.6)	72 (90.0)	
Disease duration before admission (weeks)		17.65±4.83	16.63±5.29	16.26±5.27	16.60±5.48	0.55
Family history of diabetes	No	22 (40.7)	14 (32.6)	17 (32.1)	23 (28.8)	0.54
	Yes	32 (59.3)	29 (67.4)	36 (67.9)	57 (71.3)	
Psychiatric family history	No	35 (64.8)	33 (76.7)	29 (54.7)	52 (65.0)	0.17
	Yes	19 (35.2)	10 (23.3)	24 (45.3)	28 (35.0)	
Waist-to-hip ratio		0.82±0.06	0.82±0.06	0.83±0.05	0.82±0.05	0.20
Waist-to-hip ratio (female)		0.77±0.02	0.77±0.02	0.77±0.02	0.77±0.02	0.78
Waist-to-hip ratio (male)		0.86±0.04	0.85±0.04	0.87±0.03	0.86±0.04	0.31
Fasting blood glucose		5.50±0.44	5.44±0.36	5.30±0.42	5.43±0.42	0.10
Postprandial blood glucose		6.98±0.54	6.93±0.6	7.03±0.39	7.11±0.53	0.29
TG		1.56±0.06	1.57±0.06	1.56±0.10	1.57±0.07	0.74
Cholesterol		5.03±0.15	4.98±0.23	4.98±0.17	5.01±0.19	0.35
LDL-C		2.62±0.31	2.58±0.30	2.70±0.30	2.64±0.43	0.40
HDL-C		1.48±0.18	1.52±0.23	1.48±0.22	1.48±0.21	0.82
Prolactin		19.94±7.11	9.53±6.72	16.49±8.01	14.41±7.40	<.001

Note: Group A, no occurring clozapine-induced prediabetes/diabetes; Group B, occurring clozapine-induced prediabetes with abnormally high blood sugar under control by metformin; Group C, occurring clozapine-induced prediabetes with their abnormally high blood sugar not controlled by metformin but without progression to diabetes; and group D, occurring clozapine-induced prediabetes or diabetes with abnormally high blood sugar not controlled by metformin, and with prediabetes progressing into diabetes. TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

4. Discussion

This study demonstrated that clozapine-induced prediabetes/diabetes was highly prevalent in patients with schizophrenia E-TR subtype. Most patients that incurred clozapine-induced prediabetes/diabetes showed no response to metformin treatment, with a high incidence of metformin-resistant prediabetes/diabetes. Switching to clozapine had low therapeutic effectiveness, but high metabolic side effects, when treating schizophrenia E-TR subtype. Clozapine-induced metformin-resistant prediabetes/diabetes was identified as an independent risk factor significantly associated with the reduced clinical efficacy of clozapine.

The incidence of clozapine-induced prediabetes/diabetes was particularly high in the specific subtype of schizophrenia assessed in the current study. This phenomenon could be explained by young adult patients with resistance to antipsychotic treatment having certain pathological and epidemiological risk factors for prediabetes/diabetes. Furthermore, clozapine is a confirmed antipsychotic that is associated with an extremely high incidence of antipsychotic-induced prediabetes/diabetes. Also, patients with schizophrenia E-TR subtype needed long-term high-dose treatment with clozapine to alleviate the psychotic symptoms.

The current study indicated that the efficiency of metformin in preventing clozapine-induced prediabetes/diabetes was unsatisfactory, with just 24.43% of patients responding to metformin. Metformin is a cost-effective medication used to treat patients with diabetes. Its use is recommended in patients to prevent prediabetes/diabetes, including schizophrenia patients (Misiak et al., 2020; Takayanagi et al., 2020; Foley et al., 2016; Strassnig et al., 2017; Grajales et al., 2019; Hasnain 2016; Hasnain 2015; Firestone 2005; Wu et al., 2008; Madsen et al., 2019; Tao et al., 2020). In particular, the guidelines of the British Association for Psychopharmacology (BPA) recommend the use of metformin to prevent pre-diabetes in schizophrenia patients (Cooper et al., 2016). Yet, the effects of metformin at preventing clozapine-induced prediabetes/diabetes in patients with schizophrenia E-TR subtype have not been investigated. This low efficiency indicates that the used of metformin to prevent clozapine-induced prediabetes/diabetes should be reconsidered, at least in schizophrenia patients with E-TR subtype. Given recent findings demonstrating that the use of liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) analog with anti-hyperglycemic activity (Svensson et al., 2019; Larsen et al., 2017), combined with a healthy life style (including physical exercise and strict diet control) could mitigate antipsychotic-induced prediabetes/diabetes (Warrilow et al., 2020; Clemmensen et al., 2021), further studies are needed to evaluate the beneficial effects of life style interventions at preventing clozapine-induced prediabetes/diabetes in schizophrenia E-TR subtype patients.

Switching to the clozapine strategy has been highly recommended for treating TRS in well-respected guidelines, including American Psychiatric Association and BAP. However, the clinical efficacy of clozapine in treating TRS remains unsatisfactory (Wells and McCormack 2020; Cooper et al., 2016; Kravariti et al., 2019; Kim et al., 2020; Akudjedu et al., 2020; Chan et al., 2020; Okhuijsen-Pfeifer et al., 2020; Dong et al., 2019; Yulug et al., 2020; Vergoossen et al., 2020). The current cohort study demonstrated that the psychotic symptoms of a small proportion (16.52%) of patients improved after treatment with clozapine (mean dosage, 747.05 mg per day). The exact reasons for this low efficacy of clozapine in E-TR schizophrenia could not be clarified. Previous studies comparing the clinical features of E-TR and L-TR subtypes showed that patients with schizophrenia E-TR subtype presented more severe psychopathology and poorer neuropsychological functions (Wells and McCormack 2020; Akudjedu et al., 2020; Okhuijsen-Pfeifer et al., 2020; Vergoossen et al., 2020; Kordestani-Moghadam et al., 2020; Caliskan et al., 2021). Existing studies on TRS patients of any subtype also reported impairment to cognition and abnormal changes to brain structure and function (e.g., deficits to the structural volume of brain sub-cortical, thalamus, and hippocampus structures) (Akudjedu et al., 2020; Chan et al., 2020; Yulug et al., 2020; Vergoossen et al., 2020; Kordestani--Moghadam et al., 2020; Naguy and El-Sori 2018). Thus, the low efficacy of clozapine in schizophrenia E-TR subtype could be attributed to these factors.

The efficacy of antipsychotics might also be adversely affected by antipsychotic-related complications (Dong et al., 2019; Yulug et al., 2020; Vergoossen et al., 2020). Antipsychotics induce metabolic side effects (e.g., disturbance to glucose and lipid metabolism). For example, prediabetes was reported to cause hippocampus volume to shrink (Balcioglu et al., 2020; Kordestani-Moghadam et al., 2020; Caliskan et al., 2021; Bioque et al., 2020; Thomas et al., 2017). Another study of a population with population with prediabetes/ metabolic syndrome and diabetes detected olfactory dysfunction, which was associated with

Table 2.
Logistic regression analysis of factors associated with clinical efficacy of clozapine based on the total PANSS score.

A: Univariate logistic regression analysis of factors associated with clinical efficacy based on the PANSS score						
		No-improvement (N=163)	Partial improvement (N=29)	Improvement (N=38)	OR (95% CI)	*P* value
Sex	Male	99 (73.3)	18 (13.3)	18 (13.3)	1.0	0.24
	Female	64 (67.4)	11 (11.6)	20 (21.1)	1.40 (0.80-2.47)	
Age		23.18±1.58	23.21±1.63	23.24±1.57	1.02 (0.85-1.22)	0.83
Education level (Years)	≤12	19 (73.1)	3 (11.5)	4 (15.4)	1.0	0.80
	>12	144 (70.6)	26 (12.7)	34 (16.7)	1.13 (0.46-2.78)	
Disease duration before admission (weeks)		16.69±5.19	17.52±5.38	16.55±5.43	1.01 (0.95-1.06)	0.82
Family history of diabetes	No	45 (59.2)	10 (13.2)	21 (27.6)	1.0	0.003
	Yes	118 (76.6)	19 (12.3)	17 (11.0)	0.41 (0.23-0.74)	
Psychiatric family history	No	107 (71.8)	20 (13.4)	22 (14.8)	1.0	0.56
	Yes	56 (69.1)	9 (11.1)	16 (19.8)	1.19 (0.67-2.13)	
Waist-to-hip ratio (WHR)		0.82±0.05	0.83±0.05	0.82±0.05	0.83 (0.01-155.48)	0.95
Fasting blood glucose		5.40±0.42	5.49±0.39	5.45±0.42	1.51 (0.76-2.97)	0.24
Postprandial blood glucose		7.02±0.5	7.07±0.45	7.03±0.67	1.07 (0.62-1.85)	0.81
TG		1.56±0.08	1.59±0.05	1.55±0.07	1.02 (0.02-43.82)	0.99
Cholesterol		4.99±0.18	4.98±0.21	5.05±0.18	2.53 (0.49-13.09)	0.27
LDL-C		2.62±0.33	2.71±0.53	2.67±0.28	1.54 (0.70-3.38)	0.28
HDL-C		1.50±0.22	1.51±0.20	1.43±0.14	0.41 (0.10-1.69)	0.22
Prolactin		15.42±7.80	12.90±8.73	16.50±8.63	1.00 (0.96-1.03)	0.92
Occurrence of waist-hip ratio fat during treatment	No	36 (46.8)	16 (20.8)	25 (32.5)	1.0	<.001
	Yes	127 (83.0)	13 (8.5)	13 (8.5)	0.18 (0.10-0.33)	
Occurrence of hypertriglyceridemia during treatment	No	33 (42.9)	19 (24.7)	25 (32.5)	1.0	<.001
	Yes	130 (85.0)	10 (6.5)	13 (8.5)	0.15 (0.08-0.27)	
Occurrence of hypercholesterolemia during treatment	No	53 (50.5)	22 (21.0)	30 (28.6)	1.0	<.001
	Yes	110 (88.0)	7 (5.6)	8 (6.4)	0.14 (0.07-0.28)	
With prolactin >80 ug/l during treatment	No	44 (60.3)	14 (19.2)	15 (20.5)	1.0	0.03
	Yes	119 (75.8)	15 (9.6)	23 (14.6)	0.52 (0.29-0.93)	
Total dose of clonazepam in 16 weeks		491.14±195.48	571.24±138.51	534.74±158.18	2.26 (1.08-4.74) ¶	0.03
Total dose of promethazine in 16 weeks		927.42±479.42	1077.24±361.97	1077.37±386.92	2.23 (1.22-4.09) ¶	0.01
Total dose of antipsychotic drugs in 16 weeks		80869.94±13966.14	85393.10±7762.45	84678.95±7605.05	12.57 (0.99-160.42) ¶	0.05
Prediabetes/diabetes subgroup	Group A	28 (51.9)	8 (14.8)	18 (33.3)	1.0	
	Group B	27 (62.8)	10 (23.3)	6 (14.0)	0.54 (0.24-1.19)	0.13
	Group C	46 (86.8)	2 (3.8)	5 (9.4)	0.16 (0.06-0.41)	<.001
	Group D	62 (77.5)	9 (11.3)	9 (11.3)	0.29 (0.14-0.60)	<.001
B: Correlation between clinical efficacy of clozapine and clozapine-induced prediabetes/diabetes based on the PANSS score by multivariate logistic regression model						
					OR (95% CI)	*P value*
Crude				Group B (vs. Group A)	0.54 (0.24-1.19)	0.13
				Group C (vs. Group A)	0.16 (0.06-0.41)	<.001
				Group D (vs. Group A)	0.29 (0.14-0.60)	<.001
Adjusted for age, sex				Group B (vs. Group A)	0.55 (0.25-1.22)	0.14
				Group C (vs. Group A)	0.16 (0.06-0.40)	<.001
				Group D (vs. Group A)	0.29 (0.14-0.60)	<.001
Adjusted for age, sex, family history of diabetes				Group B (vs. Group A)	0.56 (0.25-1.27)	0.17
				Group C (vs. Group A)	0.16 (0.06-0.41)	<.001
				Group D (vs. Group A)	0.31 (0.15-0.65)	0.002
Adjusted for age, sex, family history of diabetes, total dose of psychotropic drug				Group B (vs. Group A)	0.42 (0.18-0.97)	0.04
				Group C (vs. Group A)	0.12 (0.05-0.32)	<.001
				Group D (vs. Group A)	0.24 (0.11-0.52)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug				Group B (vs. Group A)	0.32 (0.13-0.79)	0.01
				Group C (vs. Group A)	0.10 (0.04-0.27)	<.001
				Group D (vs. Group A)	0.21 (0.10-0.46)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat				Group B (vs. Group A)	0.29 (0.11-0.73)	0.01
				Group C (vs. Group A)	0.18 (0.06-0.52)	0.001
				Group D (vs. Group A)	0.19 (0.08-0.44)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat, hypertriglyceridemia, hypercholesteremia				Group B (vs. Group A)	0.24 (0.09-0.64)	0.005
				Group C (vs. Group A)	0.22 (0.08-0.65)	0.006
				Group D (vs. Group A)	0.18 (0.08-0.45)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat, hypertriglyceridemia, hypercholesteremia, higher level of prolactin (>80 ug/l)				Group B (vs. Group A)	0.24 (0.09-0.64)	0.005
				Group C (vs. Group A)	0.22 (0.08-0.64)	0.006
				Group D (vs. Group A)	0.18 (0.07-0.44)	<.001
					OR (95% CI)	*P value*
Crude				Group B (vs. Group A)	0.54 (0.24-1.19)	0.13
				Group C (vs. Group A)	0.16 (0.06-0.41)	<.001
				Group D (vs. Group A)	0.29 (0.14-0.60)	<.001
Adjusted for age, sex				Group B (vs. Group A)	0.55 (0.25-1.22)	0.14
				Group C (vs. Group A)	0.16 (0.06-0.40)	<.001

(*continued on next page*)

Table 2. (*continued*)

A: Univariate logistic regression analysis of factors associated with clinical efficacy based on the PANSS score				
No-improvement (N=163)	Partial improvement (N=29)	Improvement (N=38)	OR (95% CI)	*P* value
	Group D (vs. Group A)		0.29 (0.14-0.60)	<.001
Adjusted for age, sex, family history of diabetes	Group B (vs. Group A)		0.56 (0.25-1.27)	0.17
	Group C (vs. Group A)		0.16 (0.06-0.41)	<.001
	Group D (vs. Group A)		0.31 (0.15-0.65)	0.002
Adjusted for age, sex, family history of diabetes, total dose of psychotropic drug	Group B (vs. Group A)		0.42 (0.18-0.97)	0.04
	Group C (vs. Group A)		0.12 (0.05-0.32)	<.001
	Group D (vs. Group A)		0.24 (0.11-0.52)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug	Group B (vs. Group A)		0.32 (0.13-0.79)	0.01
	Group C (vs. Group A)		0.10 (0.04-0.27)	<.001
	Group D (vs. Group A)		0.21 (0.10-0.46)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat	Group B (vs. Group A)		0.29 (0.11-0.73)	0.01
	Group C (vs. Group A)		0.18 (0.06-0.52)	0.001
	Group D (vs. Group A)		0.19 (0.08-0.44)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat, hypertriglyceridemia, hypercholesteremia	Group B (vs. Group A)		0.24 (0.09-0.64)	0.005
	Group C (vs. Group A)		0.22 (0.08-0.65)	0.006
	Group D (vs. Group A)		0.18 (0.08-0.45)	<.001
Adjusted for age, sex, family history of diabetes, total dose of clonazepam/ trimeprazine/psychotropic drug, waist hip ratio fat, hypertriglyceridemia, hypercholesteremia, higher level of prolactin (>80 ug/l)	Group B (vs. Group A)		0.24 (0.09-0.64)	0.005
	Group C (vs. Group A)		0.22 (0.08-0.64)	0.006
	Group D (vs. Group A)		0.18 (0.07-0.44)	<.001

Note: Group A, no occurring clozapine-induced prediabetes/diabetes; Group B, occurring clozapine-induced prediabetes with their abnormally high blood sugar under control by metformin; Group C, occurring clozapine-induced prediabetes with abnormally high blood sugar not controlled by metformin but without progression to diabetes; and group D, occurring clozapine-induced prediabetes or diabetes with abnormally high blood sugar not controlled by metformin, and with prediabetes progressing into diabetes.

LOCF, last observation carried forward; OR, odds ratio; CI, confidence interval; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

¶ Calculated after logarithm transformation.

Table 3.
Multivariate logistic regression analysis of clinical efficacy based on the PANSS score.

		OR (95% CI)	*P* value
Age		1.08 (0.86-1.36)	0.49
Sex (Female vs. male)		1.35 (0.67-2.72)	0.39
Family history of diabetes (Yes vs. no)		0.43 (0.21-0.85)	0.02
Occurrence of waist hip ratio fat during treatment		0.44 (0.18-1.09)	0.08
Occurrence of hypertriglyceridemia during treatment		0.33 (0.13-0.88)	0.03
Occurrence of hypercholesterolemia during treatment		0.42 (0.16-1.08)	0.07
With prolactin >80 ug/l during treatment		0.89 (0.41-1.92)	0.77
Total dose of clonazepam in 16 weeks		1.19 (0.37-3.84) ¶	0.78
Total dose of promethazine in 16 weeks		1.95 (0.75-5.07) ¶	0.17
Total dose of antipsychotic drugs in 16 weeks		9.76 (0.44-215.56) ¶	0.15
Prediabetes/diabetes subgroup	Group B (vs. Group A)	0.24 (0.09-0.64)	0.005
	Group C (vs. Group A)	0.22 (0.08-0.64)	0.006
	Group D (vs. Group A)	0.18 (0.07-0.44)	<.001

Note: Group A, no occurring clozapine-induced prediabetes/diabetes; Group B, occurring clozapine-induced prediabetes with abnormally high blood sugar under control by metformin; Group C, occurring clozapine-induced prediabetes with abnormally high blood sugar not controlled by metformin but without progression to diabetes; and group D, occurring clozapine-induced prediabetes or diabetes with abnormally high blood sugar not controlled by metformin, and with prediabetes progressing into diabetes.

LOCF, last observation carried forward.

OR, odds ratio; CI, confidence interval.

¶ Calculated after the logarithm transformation.

impaired memory (Balcioglu et al., 2020; Okhuijsen-Pfeifer et al., 2020; Dong et al., 2019; Caliskan et al., 2021). Furthermore, pre-diabetes/metabolic syndrome has been associated with fewer connections and the weaker organization of white matter networks (Mitchell et al., 2013; Vergoossen et al., 2020; Caliskan et al., 2021; Chrétien et al., 2020; Bioque et al., 2020; Anderson et al., 2015; Perry et al., 2016; Holt et al., 2005). All of these brain regions contribute to brain functioning. Therefore, prediabetes/diabetes-related brain impairment could represent a contributing factor to the reduced clinical efficacy of antipsychotics. In addition, prediabetes-induced inflammatory mediators disrupt brain metabolism (Caliskan et al., 2021; Chrétien et al., 2020), damaging white matter and impairing brain function. Consequently, the convergence of these risk factors could increase the difficulty of treating such patients (Balcioglu et al., 2020; Vergoossen et al., 2020; Kordestani-Moghadam et al., 2020; Anderson et al., 2015). Thus, we postulated that the poor clinical efficacy of clozapine in treating patients with schizophrenia E-TR subtype involves both innate and acquired factors, which might reciprocally deteriorate, hindering treatment in these patients (Balcioglu et al., 2020; Mitchell et al., 2013; Vergoossen et al., 2020).

Previous studies reported that treatment resistant schizophrenia usually accompanied with many risk factors, such as high blood glucose, high lipids, et al. However, to the best of our knowledge, rare studies reported that why some patients with early treatment resistant schizophrenia did not respond and what might have caused the blood sugar to become worsen in some of these patients despite the add-on metformin treatment. Simultaneously, few studies have evaluated the efficacy of clozapine and incidence of clozapine-induced pre-diabetes/diabetes in schizophrenia E-TR subtype. Barber et al. reported that, schizophrenia patients with their first episode of psychotic symptoms occurring in early adulthood (usually before age 25) were more likely to develop treatment resistance compared to the late onset patients with schizophrenia (Asher et al.,2021; Baptista et al., 2007). Unfortunately, as many as 40%~70% of patients with treatment-resistant schizophrenia

did not respond to the antipsychotic treatment with clozapine, despite adequate blood levels of clozapine were achieved (Campana et al., 2021; Cipriani et al.,2009). Notably, some schizophrenia patients did not respond to the antipsychotic treatment with clozapine in combination with two or three antipsychotic agents, and these patients were defined ultra-treatment resistant schizophrenia patients. Until now, it is still unclear about the mechanisms to explain why such schizophrenia patients did not respond to clozapine treatment. Although clozapine is a very old and classical antipsychotic agent, its therapeutic effect of alleviating the symptoms of schizophrenia remain largely unknown. According to previous studies, as low as 30% schizophrenia patients can be fully alleviated, while as many as 40%-70% patients cannot acquire ideally efficacy. With the existing findings, Harrow et al. at the Department of Psychiatry, University of Illinois at Chicago (Chicago, IL, USA) made the following comment "Long-term antipsychotic treatment of schizophrenia: does it help or hurt over a 20-year period?" (Harrow et al.,2018). These important studies, including ours, converged to indicate that schizophrenia is a refractory disease with unclear reason for the treatment refractory although research has spanned nearly 50 years. A number of previous studies provided evidence to support that the mechanisms of the treatment resistant of schizophrenia may involve genetic characteristics, developmental environment in the early age, gene pharmacology, et al. In the next decade, the areas in schizophrenia research and treatment are predicted to be the "hot spot" within the field of psychiatry (Doménech-Matamoros et al.,2021; Pillinger et al., 2017).

More awfully, until now, rare study reported that what might have caused the blood sugar to become worsen in some of these patients despite the add-on metformin treatment. To the best of our knowledge, the exact mechanisms underlying antipsychotic agents caused the blood sugar to become worsen in patients with schizophrenia although the add-on metformin treatment remain unclear. Currently, it has been hypothesized or postulated that insulin counter-regulatory factors, fibrinogen, and C-reactive protein (CRP) drastically reduced the effect of metformin in the treatment of olanzapine-induced high blood sugar. Doménech-Matamoros et al. reported that high blood sugar as an important index for diagnosis criteria of atypical antipsychotics-induced metabolic syndrome, play a key role in triggering the metabolic syndrome and reciprocal deteriorate with the blood lipids, anticholinergic, anti-dopaminergic effects, extrapyramidal syndromes, neuroleptic malignant syndrome, hypotension, arrhythmias, sedation, hypovitaminosis D, increased prolactin, sexual dysfunction, and sleep disturbance in the patients with schizophrenia, and ultimately caused cardiovascular and cerebrovascular events(Grajales et al., 2019; Howes et al.,2021). The findings of these two important studies indicated that antipsychotic agents induced a cascade which caused metabolic syndrome and further deteriorate the prognosis of the patients with schizophrenia, in which the antipsychotic agents-induced high blood sugar and high lipids play key role in the metabolic syndrome and the treatment resistance (Masuda et al.,2019; Meyer et al., 2009). The above-mentioned cascade reaction and the enrolled factors may contribute to the reduction or even loss of effectiveness of metformin in normalization of the abnormally high blood sugar levels (Newcomer et al., 2005). It has to be pointed out that this postulation was made on the basis of a few previous studies, and that more studies should be conducted to clarify it in the future study.

Moreover, some patients received electroconvulsive therapy (ECT) but the impact of such treatment was not discussed. Likewise, the effect of traditional Chinese medications treating hyperprolactinemia on these parameters was not discussed. However, the present study was mainly focused on investigating effects of clozapine treatment on metformin-resistant prediabetes/diabetes in patients with early treatment-resistant schizophrenia and the clinical efficacy of metformin in preventing the progress of prediabetes. To achieve the aims, we mainly monitored the alterations of blood sugar and the effect of metformin in the patients who occurred prediabetes/diabetes. We did not pay enough attention on the influences of ECT and traditional Chinese medication on blood sugar and the effect of metformin in the patients who occurred prediabetes/diabetes. A control group should be set to avoid the potential impact of ECT and traditional Chinese medication. We will take these factors into consideration to clearly clarify the influence of ECT and Chinese medication on blood sugar and the effect of metformin in the patients who occurred prediabetes/diabetes, although it is difficult to add this control group in the human study.

Some scholars maybe think that"how ethically it is feasible, a group of patients receiving clozapine but not metformin would have provided information on how high the blood glucose could be without metformin in such a population to accurately claim that metformin was not effective. It is possible that metformin was still reducing the increase in blood glucose induced by clozapine." In this study, we carefully monitored the alterations of blood sugar each week. Once prediabetes/diabetes were identified, the patients received the treatment. Hence, we did not set a group of patients who occurred high the blood sugar but did not receive metformin treatment. In the future study, we will recruit an additional group in the future study to clarify it. In addition, the impact of hypertriglyceridemia in these patients needs to be discussed whether that could be due to clozapine and whether that may contribute to the increased blood sugar. About this question, Doménech-Matamoros et al. reported that clozapine-induced hypertriglyceridemia also contributes to the increased blood sugar. However, the impact of hypertriglyceridemia in this population needs further investigation as to whether that could be due to clozapine and whether that may contribute to the increased blood sugar.

5. Limitation

This study had several limitations. First, the ages of enrolled patients ranged between 20 and 25 years in age; consequently, the results might not be representative of patients with schizophrenia E-TR subtype from other age groups. Second, the study subjects were hospitalized patients with schizophrenia E-TR subtype; consequently, these patients might have had insufficient physical activity, with inactivity on wards potentially increasing the risk of metabolic disorders (e.g., prediabetes/diabetes) and exacerbating mental health decline. As such, the findings might not reflect the status of the entire population of patients with schizophrenia E-TR subtype.

6. Conclusions

In conclusion, clozapine-induced metformin-resistant prediabetes/diabetes is highly prevalent in patients with schizophrenia E-TR subtype. Switching to clozapine treatment benefited a small proportion of patients with E-TR subtype; however, the clinical efficacy of this approach proved unsatisfactory. In particular, clozapine-induced metformin-resistant prediabetes/diabetes was identified as an independent factor that was significantly associated with the reduced efficacy of clozapine treatment in patients with schizophrenia E-TR subtype. As such, this study provides new evidence supporting the need to reconsider guidelines that recommend switching to the clozapine strategy for TRS, especially schizophrenia E-TR subtype patients. This study also confirmed the unsatisfactory effect of metformin in the glycemic control of clozapine-induced prediabetes/diabetes. Considering that good life style is vital for glycemic control, the beneficial effects of a balanced diet and physical activity in clozapine-induced prediabetes/diabetes of patients with schizophrenia E-TR subtype should be evaluated in future studies.

Author's statement

I certify that all authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere. The following declarations are also included in this statement:

Ethic

The study protocol was reviewed and approved by the Ethic Committee of Tianjin Kangtai Hospital (Tianjin, China). This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation.

Funding

This study was supported by the National Natural Science Foundation of China (81871052 to CJZ, 81801679 and 81571319 to YX), the Key Projects of the Natural Science Foundation of Tianjin, China (17JCZDJC35700 to CJZ), the Tianjin Health Bureau Foundation (2014KR02 to CJZ), the Talent Fund of Tianjin Anding (to CJZ). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author contributions

Dr. Chuanjun Zhuo had full access to the data in this study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Haibo Wang and Yong Xu contributed equally to this study, and they served as co–first authors.

Concept and design: Chuanjun Zhuo, Yong Xu, and Hailin Shao.

Acquisition, analysis, or interpretation of data: Hongjun Tian Jiayue Chen, Jie Liu, Tao Fang, Cong Yao, Weiliang Yang, Qianchen Li, Huan Mao, Anqu Yang, Jian Liu, Xiaocui Yu, Ranli Li, Shuli Xu, Bo Li, Hailin Shao, and Yuhui Chen.

Drafting of the manuscript: Hongjun Tian, Chuanjun Zhuo and Haibo Wang.

Critical revision of the manuscript for important Intellectual content: Chuanjun Zhuo, Haibo Wang, Yong Xu, and Chunhua Zhou.

Statistical analysis: Haibo Wang and Chuanjun Zhuo.

Obtained funding: Chuanjun Zhuo, Yong Xu, Guoyong Huang, Chongguang Lin

Administrative, technical, or material support: Anqu Yang, Hongjun Tian, Bo Li, and Yuhui Chen.

Supervision: Haibo Wang, Yongguo Huo and Chuanjun Zhuo.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.023.

References

Addington, D., Abidi, S., Garcia-Ortega, I., Honer, W.G., Ismail, Z., 2017. Canadian guidelines for the assessment and diagnosis of patients with schizophrenia spectrum and other psychotic disorders. Can. J. Psychiatry 62, 594–603.

Akudjedu, T.N., Tronchin, G., McInerney, S., Scanlon, C., Kenney, J.P.M., McFarland, J., et al., 2020. Progression of neuroanatomical abnormalities after first-episode of psychosis: a 3-year longitudinal sMRI study. J. Psychiatr. Res. 130, 137–151.

Anderson, V.M., McIlwain, M.E., Kydd, R.R., Russell, B.R., 2015. Does cognitive impairment in treatment-resistant and ultra-treatment-resistant schizophrenia differ from that in treatment responders? Psychiatry Res. 230, 811–818.

Andreassen, O.A., 2017. Diabetes and schizophrenia-new findings for an old puzzle. Am. J. Psychiatry 174, 616–617.

Asher, L., Birhanu, R., Baheretibeb, Y., Fekadu, A., 2021. Medical treatments are also part of God's gift": holy water attendants' perspectives on a collaboration between spiritual and psychiatric treatment for mental illness in Ethiopia. Transcult. Psychiatry 25, 13634615211015082.

Balcioglu, Y.H., Gokcay, H., Yesilkaya, U.H., 2020. One plus one sometimes equals more than two: long-acting injectable aripiprazole adjunction in clozapine-resistant schizophrenia. Clin. Neuropharmacol. 43, 166–168.

Baptista, T., Sandia, I., Lacruz, A., Rangel, N., de Mendoza, S., Beaulieu, S., Contreras, Q., Galeazzi, T., Vargas, D., 2007. Insulin counter-regulatory factors, fibrinogen and C-reactive protein during olanzapine administration: effects of the antidiabetic metformin. Int. Clin. Psychopharmacol. 22, 69–76.

Barnes, T.R., Drake, R., Paton, C., Cooper, S.J., Deakin, B., Ferrier, I.N., et al., 2020. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. J. Psychopharmacol. 34, 3–78.

Bioque, M., Parellada, E., García-Rizo, C., Amoretti, S., Fortea, A., Oriolo, G., et al., 2020. Clozapine and paliperidone palmitate antipsychotic combination in treatment-resistant schizophrenia and other psychotic disorders: a retrospective 6-month mirror-image study. Eur. Psychiatry 63, e71.

Borrelli, E.P., Lee, E.Y., Caffrey, A.R., 2020. Clozapine and hematologic adverse reactions: impact of the Risk Evaluation and Mitigation Strategy program. Ment. Health Clin. 10, 70–75.

Caliskan, A.M., Karaaslan, M., Inanli, I., Caliskan, S., Arslan, M., Esra Cicek, I., et al., 2021. The effects of adding long-acting injectable antipsychotic drugs to clozapine on relapse and hospitalization in patients with treatment-resistant schizophrenia: a mirror-image retrospective study. Int. Clin. Psychopharmacol. 36, 30–33.

Campana, M., Falkai, P., Siskind, D., Hasan, A., Wagner, E., 2021. Characteristics and definitions of ultra-treatment-resistant schizophrenia - a systematic review and meta-analysis. Schizophr. Res. 228, 218–226.

Chan, S.K.W., Chan, H.Y.V., Honer, W.G., Bastiampillai, T., Suen, Y.N., Yeung, W.S., et al., 2020. Predictors of treatment-resistant and clozapine-resistant schizophrenia: a 12-year follow-up study of first-episode schizophrenia-spectrum disorders. Schizophr. Bull.

Chrétien, B., Fedrizzi, S., Lelong-Boulouard, V., Sassier, M., Alexandre, J., Dolladille, C., 2020. Could N-acetylcysteine improve the safety of clozapine? Hum. Psychopharmacol.

Cipriani, A., Boso, M., Barbui, C., 2009. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst. Rev. 8, CD006324 https://doi.org/10.1002/14651858.CD006324.pub2.B.

Clemmensen, K.K.B., Blond, M.B., Amadid, H., Bruhn, L., Vistisen, D., Karstoft, K., et al., 2021. No effects of dapagliflozin, metformin or exercise on plasma glucagon concentrations in individuals with prediabetes: a post hoc analysis from the randomized controlled PRE-D trial. Diabetes Obes. Metab. 23, 530–539.

Cernea, S., Dima, L., Correll, C.U., Manu, P., 2020. Pharmacological management of glucose dysregulation in patients treated with second-generation antipsychotics. Drugs 80, 1763–1781. https://doi.org/10.1007/s40265-020-01393-x.

Cooper, S.J., Reynolds, G.P., Barnes, T., England, E., Haddad, P.M., Heald, A., et al., 2016. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J. Psychopharmacol. 30, 717–748.

Copeland, L.A., Parchman, M.L., Zeber, J.E., Lawrence, V.A., Downs, J.R., Miller, A.L., 2010. Prediabetes assessment and follow-up in older veterans with schizophrenia. Am. J. Geriatr. Psychiatry 18, 887–896.

Correll, C.U., Sikich, L., Reeves, G., Johnson, J., Keeton, C., Spanos, M., et al., 2020. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. World Psychiatry 19, 69–80.

de Boer, N., Guloksuz, S., van Baal, C., Willebrands, L., Deenik, J., Vinkers, C.H., et al., 2021. Study protocol of a randomized, double-blind, placebo-controlled, multi-center trial to treat antipsychotic-induced weight gain: the Metformin-Lifestyle in antipsychotic users (MELIA) trial. BMC Psychiatry 21, 4.

Dong, S., Dongwei, L., Zhang, J., Liang, J., Sun, Z., Fang, J., 2019. Individuals in the prediabetes stage exhibit reduced hippocampal tail volume and executive dysfunction. Brain Behav. 9, e01351.

Firestone, A., 2005. Weight gain and diabetes with "second-generation" antipsychotic drugs. Med. J. Aust. 182, 652–653.

Flanagan, R.J., Lally, J., Gee, S., Lyon, R., Every-Palmer, S., 2020. Clozapine in the treatment of refractory schizophrenia: a practical guide for healthcare professionals. Br. Med. Bull. 135, 73–89.

Foley, D.L., Mackinnon, A., Morgan, V.A., Watts, G.F., Castle, D.J., Waterreus, A., et al., 2016. Awareness of Pre-diabetes or Diabetes and Associated Factors in People With Psychosis. Schizophr. Bull. 42, 1280–1289.

Grajales, D., Ferreira, V., Valverde Á, M., 2019. Second-generation antipsychotics and dysregulation of glucose metabolism: beyond weight gain. Cells 8.

Harrow, M., Jobe, T.H., 2018. Long-term antipsychotic treatment of schizophrenia: does it help or hurt over a 20-year period? World Psychiatry 17, 162–163.

Hasnain, M., 2015. Genetic vulnerability in antipsychotic drug-induced diabetes. Lancet Psychiatry 2, 1049–1051.

Hasnain, M., 2016. Schizophrenia and metabolic dysregulation: shared roots? Lancet Psychiatry 3, 1003–1005.

Holt, R.I., Bushe, C., Citrome, L., 2005. Diabetes and schizophrenia 2005: are we any closer to understanding the link? J. Psychopharmacol. 19, 56–65.

Huo, L., Lu, X., Wu, F., Huang, X., Ning, Y., Zhang, X.Y., 2021. Diabetes in late-life schizophrenia: prevalence, factors, and association with clinical symptoms. J. Psychiatr. Res. 132, 44–49.

Howes, O.D., Thase, M.E., Pillinger, T., 2021. Treatment resistance in psychiatry: state of the art and new directions. Mol. Psychiatry 13.

Hyde, N., Dodd, S., Venugopal, K., Purdie, C., Berk, M., O'Neil, A., 2015. Prevalence of cardiovascular and metabolic events in patients prescribed clozapine: a retrospective observational, clinical cohort study. Curr. Drug Saf. 10, 125–131.

Jiang, W.L., Cai, D.B., Yin, F., Zhang, L., Zhao, X.W., He, J., et al., 2020. Adjunctive metformin for antipsychotic-induced dyslipidemia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Transl. Psychiatry 10, 117.
Keepers, G.A., Fochtmann, L.J., Anzia, J.M., Benjamin, S., Lyness, J.M., Mojtabai, R., et al., 2020. The American psychiatric association practice guideline for the treatment of patients with schizophrenia. Am. J. Psychiatry 177, 868–872.
Kim, J., Plitman, E., Iwata, Y., Nakajima, S., Mar, W., Patel, R., et al., 2020. Neuroanatomical profiles of treatment-resistance in patients with schizophrenia spectrum disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 99, 109839.
Kordestani-Moghadam, P., Assari, S., Nouriyengejeh, S., Mohammadipour, F., Pourabbasi, A., 2020. Cognitive impairments and associated structural brain changes in metabolic syndrome and implications of neurocognitive intervention. J. Obes. Metab. Syndr. 29, 174–179.
Kravariti, E., Demjaha, A., Zanelli, J., Ibrahim, F., Wise, C., MacCabe, J.H., et al., 2019. Neuropsychological function at first episode in treatment-resistant psychosis: findings from the ÆSOP-10 study. Psychol. Med. 49, 2100–2110.
Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., et al., 2016. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol. Med. 46, 3231–3240.
Lappin, J.M., Wijaya, M., Watkins, A., Morell, R., Teasdale, S., Lederman, O., et al., 2018. Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients. Schizophr. Res. 199, 367–373.
Larsen, J.R., Svensson, C.K., Vedtofte, L., Jakobsen, M.L., Jespersen, H.S., Jakobsen, M.I., et al., 2018. High prevalence of prediabetes and metabolic abnormalities in overweight or obese schizophrenia patients treated with clozapine or olanzapine. CNS Spectr. 1–12.
Larsen, J.R., Vedtofte, L., Jakobsen, M.S.L., Jespersen, H.R., Jakobsen, M.I., Svensson, C. K., et al., 2017. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry 74, 719–728.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., et al., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382, 951–962.
Liu, X., Wu, Z., Lian, J., Hu, C.H., Huang, X.F., Deng, C., 2017. Time-dependent changes and potential mechanisms of glucose-lipid metabolic disorders associated with chronic clozapine or olanzapine treatment in rats. Sci. Rep. 7, 2762.
Madsen, K.S., Chi, Y., Metzendorf, M.I., Richter, B., Hemmingsen, B., 2019. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database Syst. Rev. 12, Cd008558.
Manu, P., Correll, C.U., van Winkel, R., Wampers, M., De Hert, M., 2012. Prediabetes in patients treated with antipsychotic drugs. J. Clin. Psychiatry 73, 460–466.
Masuda, T., Misawa, F., Takase, M., Kane, J.M., Correll, C.U., 2019. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. JAMA Psychiatry 76, 1052–1062.
Mena, C., Gonzalez-Valderrama, A., Iruretagoyena, B., Undurraga, J., Crossley, N.A., 2018. Early treatment resistance in a Latin-American cohort of patients with schizophrenia. Schizophr. Res. 199, 380–385.
Meyer, J.M., Stahl, S.M., 2009. The metabolic syndrome and schizophrenia. Acta Psychiatr. Scand. 119, 4–14.
Misiak, B., Wiśniewski, M., Lis, M., Samochowiec, J., Stańczykiewicz, B., 2020. Glucose homeostasis in unaffected first-degree relatives of schizophrenia patients: a systematic review and meta-analysis. Schizophr. Res. 223, 2–8.
Mitchell, A.J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., De Hert, M., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders–a systematic review and meta-analysis. Schizophr. Bull. 39, 306–318.
Naguy, A., El-Sori, D., 2018. Metformin for antipsychotic-related metabolic syndrome in children: fact or fiction? Chin. Med. J. (Engl.) 131, 1490–1491.
Newcomer, J.W., 2005. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 19 (Suppl 1), 1–93.
Okhuijsen-Pfeifer, C., Sterk, A.Y., Horn, I.M., Terstappen, J., Kahn, R.S., Luykx, J.J., 2020. Demographic and clinical features as predictors of clozapine response in patients with schizophrenia spectrum disorders: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 111, 246–252.
Perry, B.I., McIntosh, G., Weich, S., Singh, S., Rees, K., 2016. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry 3, 1049–1058.
Pillinger, T., Beck, K., Gobjila, C., Donocik, J.G., Jauhar, S., Howes, O.D., 2017. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 74, 261–269.
Rachamallu, V., Haq, A., Song, M.M., Aligeti, M., 2017. Clozapine-induced microseizures, orofacial dyskinesia, and speech dysfluency in an adolescent with treatment resistant early onset schizophrenia on concurrent lithium therapy. Case Rep. Psychiatry 2017, 7359095.
Rajkumar, A.P., Horsdal, H.T., Wimberley, T., Cohen, D., Mors, O., Børglum, A.D., et al., 2017. Endogenous and antipsychotic-related risks for diabetes mellitus in young people with schizophrenia: a Danish population-based cohort study. Am. J. Psychiatry 174, 686–694.
Robinson, D.G., Woerner, M.G., Alvir, J.M., Geisler, S., Koreen, A., Sheitman, B., et al., 1999. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 156, 544–549.
Samara, M.T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., et al., 2016. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatry 73, 199–210.
Siskind, D., Russell, A., Gamble, C., Baker, A., Cosgrove, P., Burton, L., et al., 2020. Metabolic measures 12 months after a randomised controlled trial of treatment of clozapine associated obesity and diabetes with exenatide (CODEX). J. Psychiatr. Res. 124, 9–12.
Siskind, D.J., Russell, A.W., Gamble, C., Winckel, K., Mayfield, K., Hollingworth, S., et al., 2018. Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: a randomized controlled trial (CODEX). Diabetes Obes. Metab. 20, 1050–1055.
Somannavar, S., Ganesan, A., Deepa, M., Datta, M., Mohan, V., 2009. Random capillary blood glucose cut points for diabetes and pre-diabetes derived from community-based opportunistic screening in India. Diabetes Care. 32, 641–643.
Stokes, I., Griffiths, S.L., Jones, R., Everard, L., Jones, P.B., Fowler, D., et al., 2020. Prevalence of treatment resistance and clozapine use in early intervention services. BJPsych Open 6, e107.
Strassnig, M., Clarke, J., Mann, S., Remington, G., Ganguli, R., 2017. Body composition, pre-diabetes and cardiovascular disease risk in early schizophrenia. Early Interv. Psychiatry 11, 229–236.
Stroup, T.S., Gray, N., 2018. Management of common adverse effects of antipsychotic medications. World Psychiatry 17, 341–356.
Sun, M.J., Jang, M.H., 2020. Risk factors of metabolic syndrome in community-dwelling people with schizophrenia. Int. J. Environ. Res. Public Health 17.
Svensson, C.K., Larsen, J.R., Vedtofte, L., Jakobsen, M.S.L., Jespersen, H.R., Jakobsen, M. I., et al., 2019. One-year follow-up on liraglutide treatment for prediabetes and overweight/obesity in clozapine- or olanzapine-treated patients. Acta Psychiatr. Scand. 139, 26–36.
Takayanagi, Y., Ishizuka, K., Laursen, T.M., Yukitake, H., Yang, K., Cascella, N.G., et al., 2020. From population to neuron: exploring common mediators for metabolic problems and mental illnesses. Mol. Psychiatry.
Tao, T., Zhang, Y., Zhu, Y.C., Fu, J.R., Wang, Y.Y., Cai, J., et al., 2020. Exenatide, metformin, or both for prediabetes in PCOS: A randomized, open-labeled, parallel-group controlled study. J. Clin. Endocrinol. Metab.
Thomas, E.H.X., Bozaoglu, K., Rossell, S.L., Gurvich, C., 2017. The influence of the glutamatergic system on cognition in schizophrenia: a systematic review. Neurosci. Biobehav. Rev. 77, 369–387.
Vergoossen, L.W., Schram, M.T., de Jong, J.J., Stehouwer, C.D., Schaper, N.C., Henry, R. M., et al., 2020. White matter connectivity abnormalities in prediabetes and type 2 diabetes: the maastricht study. Diabetes Care. 43, 201–208.
Warrilow, A., Somerset, S., Pumpa, K., Fleet, R., 2020. Metformin use in prediabetes: is earlier intervention better? Acta Diabetol. 57, 1359–1366.
Wells, C., McCormack, S., 2020. Clozapine initiation for schizophrenia: a review of clinical effectiveness and guidelines. Can. Agency Drugs Technol. Health.
Westfall, N.C., Mavrides, N.A., Coffey, B.J., 2018. Multidisciplinary management of adolescent early-onset, treatment-resistant schizophrenia complicated by avoidant/restrictive food intake disorder and catatonia in acute exacerbations. J. Child Adolesc. Psychopharmacol. 28, 663–666.
Wu, R.R., Zhao, J.P., Jin, H., Shao, P., Fang, M.S., Guo, X.F., et al., 2008. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. JAMA 299, 185–193.
Wu, R.R., Zhao, J.P., Liu, Z.N., Zhai, J.G., Guo, X.F., Guo, W.B., et al., 2006. Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia. Psychopharmacology (Berl.) 186, 572–578.
Yulug, B., Saatci, O., Işıklar, A., Hanoglu, L., Kilic, U., Ozansoy, M., et al., 2020. The association between HbA1c levels, olfactory memory and cognition in normal, pre-diabetic and diabetic persons. Endocr. Metab. Immune Disord. Drug Targets 20, 198–212.
Zhang, R., Hao, W., Pan, M., Wang, C., Zhang, X., Chen, D.C., et al., 2011. The prevalence and clinical-demographic correlates of diabetes mellitus in chronic schizophrenic patients receiving clozapine. Hum. Psychopharmacol. 26, 392–396.
Zhou, Y., Song, X., Guo, Y., Lang, X., Li, Z., Zhang, X.Y., 2021. Sex differences in metabolic disorder patterns of first-episode drug-naive patients with schizophrenia. Psychoneuroendocrinology 124, 105061.
Zimbron, J., Khandaker, G.M., Toschi, C., Jones, P.B., Fernandez-Egea, E., 2016. A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome. Eur. Neuropsychopharmacol. 26, 1353–1365.