

Hypercoagulable state in patients with schizophrenia: different effects of acute and chronic antipsychotic medications

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Abstract

Background: Previous studies reported higher incidences of venous thromboembolism and cardiovascular disease in schizophrenia patients and higher indicators of thrombosis, thrombocyte activation, and platelet dysfunction.

Objectives: To check if first-episode schizophrenia (FES) patients have a hypercoagulable state and determine whether acute and chronic antipsychotics have the same effect on blood coagulation or fibrinolysis-related biomarkers.

Design: Case-control study.

Methods: A total of 81 participants were grouped in FES, chronic schizophrenia (CS), and healthy controls (HCs). In addition to demographic data and clinical characteristics, immunological analyses were performed to measure plasma levels of D-dimer, plasminogen activator inhibitor-1 (PAI-1), soluble P selectin (sP-sel), tissue plasminogen activator (tPA), thrombotic precursor protein (TpP), and von Willebrand's disease factor (vWF).

Results: Compared to HC group, FES patients showed higher PAI-1 (28.61 ng/ml *versus* 15.69 ng/ml), sP-sel (2.78 ng/ml *versus* 1.18 ng/ml), and TpP (15.61 µg/ml *versus* 5.59 µg/ml) along with a higher PAI-1/tPA (3.12 *versus* 2.00). Acute antipsychotic medication reduced higher PAI-1 (28.61 → 21.99), sP-sel (2.78 → 1.87), tPA (9.59 → 5.83), TpP (15.61 → 10.54), and vWF (383.18 → 291.08) in FES patients. However, plasma sP-sel and vWF in CS patients returned to the pre-treatment levels in FES patients, and PAI-1/tPA significantly decreased compared to FES patients.

Conclusion: These results suggest a hypercoagulable state in FES patients and demonstrate contrast effects of acute and chronic antipsychotics on coagulation or fibrinolysis in schizophrenia patients.

Keywords: antipsychotics, coagulation, hypercoagulability, schizophrenia, venous thromboembolisms

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Introduction

Schizophrenia is a chronic, severe, and disabling brain disorder with a life prevalence of approximately 1% of world population.¹ Patients with schizophrenia present positive and negative symptoms, as well as cognitive impairments that influence their thoughts, perceptions, speech, affect, and behaviors. It was estimated that people with schizophrenia die on average 20 years earlier than individuals without this illness.^{2,3} One possible

risk factor for a shortened life span in people with schizophrenia is an increased risk of venous thromboembolism (VTE)⁴ and cardiovascular disease.⁵ These risk factors are directly or indirectly associated with the use of antipsychotics. For example, the risk of VTE in people using antipsychotics is higher than the general population.⁶⁻⁸ In a population-based cohort study, the schizophrenia cohort exhibited a 2.02-fold higher adjusted hazard ratio (HR) for developing deep

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venous thrombosis (DVT), and a 1.99-fold higher adjusted HR for developing pulmonary embolism (PE) compared to the non-schizophrenia cohort. Schizophrenia patients using first- or second-generation antipsychotics exhibited a higher adjusted HR for both DVT and PE development.⁹ Patients with schizophrenia who receive long-term antipsychotic medication show evidence of an overall hypercoagulable and hypofibrinolytic state, which may contribute to their increased risk of VTE.¹⁰ According to a recent review, 87.5% of patients taking clozapine had risk factors for VTE.¹¹

In addition to the antipsychotic drug-associated VTE risk factors mentioned above, schizophrenia itself has a tendency to increase the risk of VTE, as evidenced by elevated markers of thrombosis, thrombotic cell activation, and platelet dysfunction in antipsychotic-naïve patients with schizophrenia.^{12,13} This tendency is not surprising given immobility due to avolition,¹⁴ and catatonia seen in a high proportion (9–17%) of acute schizophrenia patients.¹⁵ Moreover, schizophrenia patients are often associated with hyperglycemia, hyperlipidemia, hyperhomocysteinemia, obesity, and nicotine dependence, which are risk factors for VTE.^{16,17} However, few studies have compared the patients with first-episode schizophrenia (FES) to those with chronic schizophrenia (CS) in terms of risk factors for VTE.

This study measured and compared several biomarkers relevant to coagulation or fibrinolysis in drug-naïve FES patients, CS patients, and healthy controls (HCs) matched with age and gender. The measured biomarkers include D-dimers, plasminogen activator inhibitor-1 (PAI-1), soluble P selectin (sP-sel), tissue plasminogen activator (tPA), thrombus precursor protein (TpP), and von Willebrand factor (vWF). In addition, effects of acute and chronic antipsychotic medications on these biomarkers in the FES and CS patients were assessed and compared. We aimed to know whether there were group differences in terms of clotting and fibrinolysis-related biomarkers, and to explore the effects of acute and chronic antipsychotics on these biomarkers in patients with schizophrenia.

Materials and methods

Participants

Participants in this study were 18–45 years old and categorized into three groups of drug-naïve FES patients, CS patients, and health controls,

with 27 persons in each group. The sample size in each group was calculated by referring to a previous clinical study determining whether markers of thrombogenesis are increased in psychotic patients who have not yet been treated with antipsychotic medication. Each group of the referred study consisted of 25 participants. In the present study, we set a target power of 0.90, α value of 0.05 (two-sided). With these inputting data, the PASS 15 software (NCSS, Utah, American) figured out the sample size of 26 (persons) in each group.

The patients were hospitalized in the adult psychiatric unit of Shenzhen Kangning Hospital (SKH)/Shenzhen Mental Health Center during the period between May 2019 and May 2020, and healthy controls were adults matched for age and gender but had no history of mental disorders. All participants were informed of the purpose of the study before agreeing to participate in the study, which did not incur any additional costs to the participants.

All schizophrenia patients met the diagnostic criteria for schizophrenia as established by the DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders 5th version) or ICD-10 (International Classification of Diseases 10th version). Their Positive and Negative Symptom Scale (PANSS) scored ≥ 60 points overall and were assessed by a certificated psychiatrist Tu Weifeng (TW). Patients with FES were those admitted to the hospital (SKH) for psychotic symptoms, but had never taken antipsychotic medications or been diagnosed with schizophrenia or any mental disorder. CS patients were hospitalized for a diagnosis of schizophrenia and had a disease course of ≥ 5 years. Healthy controls had no mental disorder and no history of mental disorder in their immediate relatives. They matched with FES patients in age and sex. The exclusion criteria applied to all participants: (1) who had major physical conditions, such as gastrointestinal, liver, kidney, nervous system, blood disorders, and immune dysfunction; (2) who have been diagnosed with alcohol addiction or other psychotropic substance abuse; (3) who have undergone surgical operations within the last 3 months; (4) who are recently taking drugs that affect the hematopoietic system and regulate immune function; and (5) during pregnancy or lactation.

Study design

When enrolling in the study, all participants were asked to provide their demographic information,

as well as a history of physical illnesses and mental disorders. Their body mass index (BMI) was calculated based on body weight (kg) and height (cm). PANSS was used to evaluate the severity of clinical manifestations of FES patients on admission day. Blood sample was collected from all participants after an overnight fasting for biochemical analyses to measure levels of serum fasting glucose (SFG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG). In addition, the levels of biomarkers related to coagulation and fibrinolysis in the blood of all participants were assessed. For FES patients, two batches of biochemical analyses were done with two blood samples collected on admission day (before antipsychotic medication) and after finishing acute antipsychotic (AAP) therapy for 4–8 weeks. For CS patients and healthy controls, only one batch of biochemical analyses were performed.

Antipsychotics or drug combination used for the schizophrenia patients

During a 4–8 weeks of hospitalization, the vast majority of patients with FES were treated with only one atypical antipsychotic, whereas two patients were treated with risperidone in combination with quetiapine or olanzapine. The medical records of CS patients show that more than half of them were treated with various combinations of drugs, including risperidone plus \times (aripiprazole, clozapine, olanzapine, sulpiride, sodium valproate, or lithium). Dosage details for each drug and drug combination are shown in Table 1. In order to compare the antipsychotic dosages used in the FES and CS patients, we transferred dosages of all antipsychotics (except for risperidone) into risperidone dose equivalence, followed by statistical comparisons between the two groups of patients. The risperidone dose equivalence in the two groups were 6.94 (2.27) and 7.76 (3.34) mg/day, respectively. The difference is not statistically significant. Of note is, eight of CS patients were treated with an antipsychotic plus a mood stabilizer of either lithium or valproate in sustained release capsule. These patients did not respond well to antipsychotic(s), but did better in the combination of antipsychotic plus a mood stabilizer, which indeed reduced the dosage of the antipsychotic used for the patients as indicated by an averaged risperidone dose equivalence of 5.81 mg/day (1.70).

Biochemical and immunological analyses of blood samples

For biochemical analyses, peripheral venous blood samples (4 ml per person) were collected from cubital vein of all participants using a 21-gauge butterfly needle. SFG, LDL-C, HDL-C, TC, and TG levels were timely detected in the clinical laboratory of SKH. Plasma aliquots for other biomarkers were stored at -20°C until analyzed using commercial ELISA kits according to the protocol provided by the manufacturer (mlbio, Shanghai, China).

Statistical analysis

SPSS 25.0 (IBM, New York, American) was used for statistical analysis of all the data. The Shapiro–Wilk test was used to test the normality of a dataset. The data in normal distribution were expressed as mean \pm SD, otherwise expressed as median (interquartile range). For inter-group (FES, CS, and HCs) comparisons, the Bonferroni method was employed following one-way ANOVA. For intra-group comparisons of FES patients (before–after comparisons), paired *t*-test was done. The comparisons of medians were done by performing the Mann–Whitney *U*-test. Enumeration data were expressed as percentages and compared by chi-square test. $p \leq 0.05$ was considered statistically significant.

Results

Baseline characteristics of the participants

A total of 81 persons participated in this study, including 27 drug-naïve FES patients, 27 CS patients, and 27 healthy controls matched for age and gender. As shown in Table 2, compared with healthy controls, patients with schizophrenia had fewer years of education and a family history of the disease. The CS group had higher BMI and TG levels than the other two groups. The level of SFG in CS group was higher than that in FES patients and healthy controls, but the difference was not statistically significant. HDL levels were lower in both FES and CS patients compared to healthy controls.

Hypercoagulable state in FES patients

The first objective of this study was to determine whether FES patients had hypercoagulability relative to healthy controls. We therefore measured

Table 1. Drugs or drug combinations used for FES and CS patients.

FES patients		CS patients	
Code	Drug, dose (mg/day)	Code	Drug/drug combination, dose (mg/day)
1, 2	Amisulpride, 600	1	Clozapine, 200
3	Aripiprazole, 10	2	Clozapine, 300
4, 5	Aripiprazole, 15	3	Clozapine, 400
6, 7	Olanzapine, 10	4	Olanzapine, 10
8, 9	Olanzapine, 15	5–7	Olanzapine, 20
10–15	Olanzapine, 20	8	Paripiperidone, 150 mg/month (inj.)
		9	Risperidone, 4
16	Quetiapine, 800	10, 11	Risperidone, 5
17, 18	Risperidone, 4	12	Ziprasidone, 80
19, 20	Risperidone, 5	13	Clozapine, 350 + Risperidone, 4
21–25	Risperidone, 6	14	Aripiprazole, 5 + Risperidone, 6
26	Risperidone, 5 + Olanzapine, 10	15	Aripiprazole, 15 + Valproate (1000, sustained release)
27	Risperidone, 6 + Quetiapine, 800	16	Aripiprazole, 5 + Risperidone, 4
		17	Aripiprazole, 10 + Paripiperidone, 12
		18	Haloperidol, 4 + Haloperidol decanoate (50 mg/2 weeks, inj.)
		19	Olanzapine, 20 + Risperidone, 4
		20	Olanzapine, 15 + Lithium carbonate, (1200, sustained release)
		21	Paripiperidone, 100 mg/month (inj.) + Valproate (1000, sustained release)
		22	Quetiapine, 200 + Lithium carbonate (900, sustained release)
		23	Risperidone, 5 + Lithium carbonate (900, sustained release)
		24	Risperidone, 5 + Sulpiride, 1000
		25	Risperidone, 6 + valproate (750, sustained release)
		26, 27	Risperidone, 6 + valproate (1000, sustained release)

CS, chronic schizophrenia; FES, first-episode schizophrenia.

Table 2. Demographic information and metabolism-related data of the participants.

Variables	FES (n=27)	CS (n=27)	HC (n=27)	F/H/ χ^2	p
Age (years)	25.77 ± 5.16	27.88 ± 4.92	25.64 ± 4.58	2.376 ^a	0.100
Male [n (%)]	10 (37.04)	12 (44.44)	13 (48.10)	0.704 ^b	0.703
Education level (years)	10.55 ± 1.67	9.81 ± 2.18	15.92 ± 1.20	55.30 ^a	<0.001
Unmarried [n (%)]	23 (85.20)	19 (70.40%)	18 (66.70)	2.700 ^b	0.259
Family history [n (%)]	1 (3.70)	4 (14.80)	0 (0)	5.540 ^b	0.063
BMI (kg/m ²)	21.21 ± 2.61	24.16 ± 3.16	21.68 ± 2.02	9.666 ^a	<0.001
SFG (mM/L)	4.51 ± 0.53	4.82 ± 0.67	4.54 ± 0.53	2.332 ^a	0.104
TC (mM/L)	4.16 ± 0.70	4.27 ± 0.72	4.00 ± 1.04	0.711 ^a	0.495
TG (mM/L)	0.83 (0.56)	1.76 (0.64)	0.79 (0.78)	29.902 ^c	<0.001
HDL (mM/L)	1.21 ± 0.33	1.17 ± 0.30	1.45 ± 0.40	4.845 ^a	0.010
LDL (mM/L)	2.44 ± 0.66	2.69 ± 0.78	2.32 ± 0.63	1.985 ^a	0.144

Continuous values are presented as mean ± SD. TG data are presented as median (interquartile range). The values with superscript a resulted from one-way ANOVA (F); the values with superscript b resulted from chi square test (χ^2); the values with superscript c resulted from the Kruskal–Wallis test (H).
 BMI, body mass index; CS, chronic schizophrenia; FES, first-episode schizophrenia; HC, healthy control; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFG, serum fasting glucose; TC, total cholesterol; TG, triglycerides.

plasma levels of biomarkers associated with coagulation or fibrinolysis, including D-dimer, PAI-1, sP-sel, t-PA, TpP, and vWF. As shown in Table 3, FES patients showed higher levels of PAI-1, sP-sel, TpP, and higher PAI-1/tPA value compared to healthy controls. Higher TpP reflects active thrombosis while elevated level of sP-sel is indicative of endothelium activation. Increased PAI-1 levels indicate reduced plasmin formation. These results indicate that the FES patients in this study were in a hypercoagulable state compared to healthy controls. The two groups were comparable in terms of tPA and vWF. D-dimer concentration in FES group was marginally higher ($p=0.085$) compared to that of healthy controls.

AAP medication improved the hypercoagulable state in FES patients

The next goal of this study was to examine the effects of AAP on the coagulable state in FES patients. Thus, all FES patients ($n=27$) were treated with antipsychotics for 4–8 weeks, and biochemical analyses for the same biomarkers associated with coagulation and fibrinolysis were performed at the end of treatment. As shown in

Table 4, higher levels of PAI-1, sP-sel, and TpP in FES patients were reversed after antipsychotic therapy for 4–8 weeks. Interestingly, plasma tPA and vWF levels were significantly reduced in FES patients after acute administration of antipsychotics. But the treatment did not change D-dimer concentration and PAI-1/tPA value of the FES patients.

In addition, we compared the FES patients following AAP to healthy controls in terms of the same biomarkers mentioned above. As shown in Table 5, significant differences existed between the two groups in values of PAI-1, tPA, TpP, and PAI-1/tPA, indicating that AAP did not normalize all biomarkers relevant to coagulation and fibrinolysis in the FES patients.

Comparisons between CS and FES patients following AAP

The third goal of this study was to compare effects of acute and chronic antipsychotic medications on plasma biomarkers relevant to coagulation and fibrinolysis in schizophrenia patients. For this purpose, we compared the biomarkers of CS patients to those of FES patients before and

Table 3. Hypercoagulable state in first-episode schizophrenia patients.

Measurements	FES (n = 27)	HC (n = 27)	Z	p
D-dimers (ng/ml)	340.00 (310.00)	290.00 (170.00)	-1.52	0.085
PAI-1(ng/ml)	28.61(10.97)	15.69 (25.58)	-2.74	0.006
sP-sel (ng/ml)	2.78 (1.70)	1.18 (1.55)	-2.62	0.009
tPA (ng/ml)	9.59 (5.45)	10.20 (13.46)	-0.46	0.647
TpP (µg/ml)	15.61 (5.50)	5.59 (8.41)	-3.78	<0.001
PAI-1/tPA	3.12 (1.06)	2.00 (1.97)	-3.14	0.002
vWF (pg/ml)	383.18 (196.36)	403.33 (476.53)	-0.71	0.473

Data are presented as median (interquartile range). Z values resulted from the Mann-Whitney *U*-test. FES, first-episode schizophrenia; HC, healthy control; PAI-1, plasminogen activator inhibitor-1; sP-sel, soluble P selectin; tPA, tissue plasminogen activator; TpP, thrombus precursor protein; vWF, von Willebrand factor.

Table 4. Acute antipsychotic medications reverse the hypercoagulable state in FES patients.

Measurements	Drug-naïve FES (n = 27)	AP for 4–8 weeks (n = 27)	Z	p
D-dimers (ng/ml)	340.00 (310.00)	300.00 (180.00)	-1.30	0.162
PAI-1 (ng/ml)	28.61(10.97)	21.99 (15.01)	-1.87	0.061
sP-sel (ng/ml)	2.78 (1.70)	1.87 (1.55)	-2.09	0.037
tPA (ng/ml)	9.59 (5.45)	5.83 (7.50)	-2.14	0.034
TpP (µg/ml)	15.61 (5.50)	10.54 (7.27)	-2.55	0.011
PAI-1/tPA	3.12 (1.06)	3.47 (1.78)	-1.35	0.178
vWF (ng/ml)	383.18 (196.36)	291.08 (246.01)	-2.09	0.037

Data are presented as median (interquartile range). Z values resulted from Mann-Whitney *U*-test. AP, antipsychotic; FES, first-episode schizophrenia; PAI-1, plasminogen activator inhibitor-1; sP-sel, soluble P selectin; tPA, tissue plasminogen activator; TpP, thrombus precursor protein; vWF, von Willebrand factor.

after AAP. As shown in Figure 1, sP-sel level in drug-naïve FES patients decreased after AAP, but it returned to the pre-treatment level in CS patients [Figure 1(a)]. Similarly, levels of PAI-1, tPA, TpP, and vWF in drug-naïve FES patients decreased after AAP but returned to pre-treatment levels in CS patients [Figure 1(b), (c), (e), (f)]. However, AAP did not change tPAI-1/tPA value in patients with FES, whereas patients with CS had a reduced tPAI-1/tPA relative to patients with FES treated with AAP [Figure 1(d)].

Discussion

The three main findings of this study are: (1) drug-naïve FES patients presented a hypercoagulable

state and vascular endothelial cell injury as evidenced by higher levels of circulating PAI-1, sP-sel, and TpP, as well as higher PAI-1/tPA ratio compared to healthy controls; (2) the AAP therapy improved the hypercoagulable state and vascular endothelial cell injury in FES patients as the treatment reduced higher plasma levels of sP-sel, TpP, and PAI-1, as well as significantly decreased levels of tPA and vWF in the patients; and (3) chronic antipsychotic therapy increased the risk of thrombosis in the patients as CS patients showed higher plasma levels of sP-sel, tPA, and vWF than FES patients who received AAP medications.

As its name implies, PAI-1 functions as the principal inhibitor of tPA and urokinase (uPA), two

Table 5. The Comparisons between patients treated with acute antipsychotic medications and healthy controls.

Measurements (reference)	HC (n=27)	AP for 4–8 weeks (n=27)	Z	p
D-dimers (0–500 ng/ml)	290.00 (170.00)	300.00 (180.00)	−0.613	0.353
PAI-1(11.00–31.00 ng/ml)	15.69 (25.58)	21.99 (15.01)	−2.119	0.034
sP-sel (1.05–3.95 ng/ml)	1.18 (1.55)	1.87 (1.55)	−0.718	0.473
tPA (4.68–13.32 ng/ml)	10.20 (13.46)	5.83 (7.50)	−2.846	0.004
TpP (4.08–13.25 μg/ml)	5.59 (8.41)	10.54 (7.27)	−2.55	0.011
PAI-1/tPA	2.00 (1.97)	3.47 (1.78)	−4.074	<0.001
vWF (256.32–515.68 ng/ml)	403.33 (476.53)	291.08 (246.01)	−0.234	0.815

Data are presented as median (interquartile range). Z values resulted from the Mann–Whitney *U*-test.

AP, antipsychotic; FES, first-episode schizophrenia; HC, healthy control; PAI-1, plasminogen activator inhibitor-1; sP-sel, soluble P selectin; tPA, tissue plasminogen activator; TpP, thrombus precursor protein; vWF, von Willebrand factor.

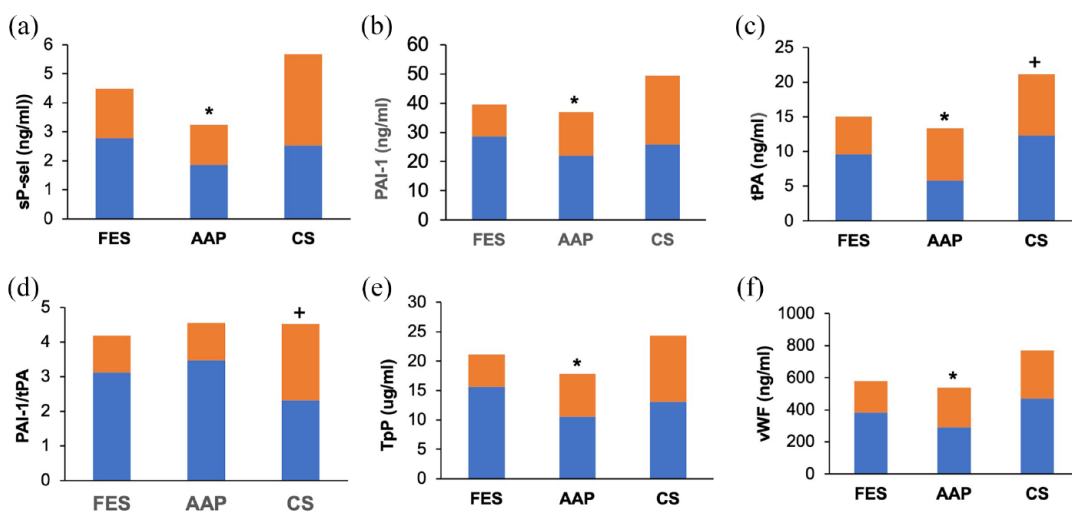


Figure 1. Different effects of acute and chronic antipsychotic medications on coagulation and fibrinolysis biomarkers in the blood of patients with schizophrenia. (a) Effects on sP-sel levels. (b) Effects on PAI-1 levels. (c) Effects on tPA levels. (d) Effects on PAI-1/tPA. (e) Effects on TpP levels. (f) Effects on vWF levels. Data are presented as median (blue) + interquartile (red). Mann–Whitney *U*-test was done to make comparisons between groups. * $p < 0.05$, compared to FES. + $p < 0.05$, compared to AAP.

AAP, acute antipsychotic treatment; CS, chronic schizophrenia patients; FES, first-episode schizophrenia patients; PAI-1, plasminogen activator inhibitor-1; sP-sel, soluble P selectin; tPA, tissue plasminogen activator; TpP, thrombus precursor protein; vWF, von Willebrand factor.

activators of plasminogen. This protease inhibitor is mainly produced from the endothelial cells. Therefore, increased plasma level of PAI-1 in drug-naïve FES patients suggests the presence of endothelial cell damage, which may increase the risk for VTE. In support of this suggestion, FES patients showed a higher PAI-1/tPA ratio.¹⁸ Indeed, elevated

PAI-1 is considered a risk factor for thrombosis and atherosclerosis, whereas PAI-1/tPA ratio has been used as an index of abnormalities in thrombosis/fibrinolysis system.¹⁹ Along with elevated PAI-1, circulating level of sP-sel in FES patients in this study was also higher than healthy controls, indicating platelet and endothelial cell activation.^{13,20}

TpP has been identified as biomarker of active thrombosis in severe clinical conditions including myocardial infarction.²¹ And TpP ELISA test had a 100% sensitivity for evaluating proximity deep thrombosis and PE.²² In the present study, we found that FES patients showed higher levels of TpP, a marker of active thrombosis. Considering the data from the aforementioned two previous studies, the changes in PAI-1 and sP-sel, plus higher levels of TpP in FES patients in this study demonstrate a hypercoagulable state in these patients.

The fibrin DD is the primary enzymatic degradation product of fibrin by plasmin. As such, a negative D-dimer is now considered the biochemical gold standard for ruling out an acute episode of VTE in a patient with a low pretest probability for VTE.²³ In this study, the concentration of D-dimer in FES group was slightly higher than that in healthy control group ($p=0.085$), but it was not significant, indicating that insignificant blood coagulation happened, at least in some patients of this group before blood collection. This explanation is consistent with previously reported elevated markers of thrombosis, thrombotic cell activation, and platelet dysfunction in patients with schizophrenia who have never taken antipsychotics.^{12,13} Of note, FES patients in this study were comparable to healthy controls in the demographic data and some clinical characteristics including age, BMI, SFG, TC, TG, and LDL, except for HDL which was lower in FES patients than controls. These data suggest that metabolic syndrome and obesity were not important contributors to the hypercoagulable state in young adult FES patients of the present study.

Although antipsychotic drugs increased VTE risk in previous studies,²⁴ few studies investigated effects of AAP agents. Of the available research, a time-matched case-control analysis with a cohort of 111,818 patients with at least one antipsychotic drug prescription is worth highlighting. This study revealed that current exposure to antipsychotic drugs was not associated with an increased risk of DVT, compared to nonusers.²⁵ Relevantly, an early study found no difference in coagulation factors between patients treated with clozapine (for 12 weeks) and the controls.²⁶ In the present study, 4–8 weeks of antipsychotic treatment effectively reduced higher levels of sP-sel, PAI-1, and TpP in patients with FES, but the PAI-1/tPA ratio did not change, suggesting that the treatment has an

anticoagulant effect. In support of this suggestion, the treatment significantly decreased levels of vWF in the patients. This finding reminds us of the major role of vWF in blood coagulation *via* binding to other proteins, particularly factor VIII, and promoting platelet adhesion to wound sites demonstrated in a previous study.²⁷ Further supporting evidence for the beneficial effects of AAP is the decreased tPA in FES patients after the treatment. This serine protease (tPA) locates in endothelial cells and catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown.²⁸ Moreover, a recent study reported the reduction of plasma procoagulant activity in patients with schizophrenia during pharmacotherapy.²⁹ Collectively, the data presented in this study, plus those reported in the above-mentioned previous studies, demonstrate a protective effect of AAP on damaged endothelial cells in FES patients thus ameliorated the hypercoagulability in the patients.

Although the mechanism of protective action of AAP therapy on damaged endothelial cells in patients with FES is unknown, the anti-inflammatory and antioxidant effects of atypical antipsychotics are noteworthy. First, accumulating evidence demonstrates that schizophrenia is characterized by mild or chronic inflammation along with disturbances in metabolism.^{30,31} Second, metabolic syndrome/overload, which are associated with schizophrenia, evokes several stress reactions, such as oxidative, inflammatory, organelle, and cell hypertrophy.³² Third, atypical antipsychotics were shown to suppress production of pro-inflammatory cytokines but upregulate interleukin-10 (an anti-inflammatory cytokine) in lipopolysaccharide-treated mice.³³ Both olanzapine and aripiprazole decreased mRNA and protein levels of IL-1 β (interleukin-1 β), IL-6, and TNF- α (tumor necrosis factor- α) in conditioned medium of stimulated primary human peripheral blood mononuclear cells from healthy donors.³⁴ Clozapine significantly increased the production of anti-inflammatory cytokines such as IL-10 and TGF- β (transforming growth factor- β) in blood leukocytes of healthy volunteers.³⁵ Fourth, atypical antipsychotics exert a strong antioxidant activity in experimental models of schizophrenia by rescuing the antioxidant system and increasing serum levels of the antioxidant enzymes superoxidase dismutase and glutathione as reviewed recently.³⁶ The anti-inflammatory actions of atypical antipsychotics, however, are not seen in patients after chronic

antipsychotic treatment which induced weight gain and metabolic side effects.³⁷

Plasma sP-sel, tPA, TpP, and vWF in CS patients recovered to levels comparable to those of antipsychotic-naïve FES patients, but higher than those of FES patients who received AAP medication. Moreover, the PAI-1/tPA ratio significantly decreased because of the significant tPA increase. These data indicate the presence of a hypercoagulable state in the CS patients. They had a course of more than 5 years and was admitted to the psychiatric hospital due to recurrent psychotic episodes. These data added further evidence that chronic antipsychotics increase the risk of developing VTE in schizophrenia patients. This conclusion is in line with previous clinical reports linking the use of antipsychotics to VTE.⁶

In explaining the beneficial effects of AAP on hypercoagulable state and vascular endothelial cell injury in FES patients and the relapse of blood hypercoagulable status in CS patients, the following issues merit special attention. First, CS patients have higher prevalence rates of co-morbidities including metabolic syndrome, diabetes, hypertension, obesity, and insulin resistance in Hagi *et al.*³⁸ On the one hand, these medical conditions are associated with the long-term use of antipsychotics, especially atypical drugs.³⁹ On the other hand, they are both risk factors for VTE and vascular injury.^{40,41} Second, smoking should not be ignored though this study did not collect the smoking-relevant information from the participants. Previous studies have reported that schizophrenia patients have extremely high prevalence of smoking compared to the general population and patients with other psychiatric diagnoses.^{42–44} And smoking has been demonstrated as a risk factor for VTE with a dose-response relationship.^{45,46} Therefore, it is plausible to suggest that smoking cessation during the hospitalization period of acute schizophrenia patients may help to ameliorate the hypercoagulable state and vascular endothelial cell injury in them, whereas re-smoking in some patients of CS group may contribute to the relapse of blood hypercoagulable status in these patients.

Limitations

The limitations of this study should not be ignored. First, the human cohort sample was relatively small. Therefore, caution should be taken in generalizing conclusions from this study.

Relevant to the relatively small sample size, we could not analyze possible differences in effects of different antipsychotic treatment on the coagulation parameters in schizophrenia patients. Third, we were unable to analyze effects of confounding factors such as smoking as mentioned above. Fourth, the activities of daily living (ADL) of schizophrenia patients in the present study was not assessed although immobility due to avolition¹⁴ is one of clinical manifestations of schizophrenia patients. This limitation disabled us to rule out the contribution of ADL to the hypercoagulable state in FES patients and the abnormalities in coagulation parameters in CS patients. Nevertheless, the existent data confirmed the pre-existing abnormalities of coagulation parameters in FES patients and demonstrated the different effects of acute and chronic administration of antipsychotics on these parameters. These findings have potential implications for the prevention and intervention of VTE in schizophrenia patients.

Conclusion

In conclusions, drug-naïve FES patients have a hypercoagulable state and vascular endothelial cell injury; AAP improves the hypercoagulable state and vascular endothelial cell injury in FES patients; chronic antipsychotic therapy increases the risk of thrombosis, which could be a secondary effect mediated by increased weight and body fat, as well as smoking.

Declarations

Ethics approval and consent to participate

The ethical aspects of this study were reviewed and approved by the Human and Animal Research Ethics Committee of the Mental Health Center, Shantou University Medical College, China (201912). All participants provided the informed consent to participating this study.

Consent for publication

All patients and healthy controls in this study consented for the publication of the data in this research relevant to the diagnosis and treatment of schizophrenia.

Author contributions

Caiji Zheng: Conceptualization; Data curation; Methodology; Project administration; Writing – original draft.

Haiyan Liu: Investigation; Methodology.

Weifeng Tu: Investigation; Project administration.

Lingyun Lin: Conceptualization; Data curation; Project administration; Supervision.

Haiyun Xu: Conceptualization; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data are available on a reasonable request.

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References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 2000.
2. Kredentser MS, Martens PJ, Chochinov HM, *et al*. Cause and rate of death in people with schizophrenia across the lifespan: a population-based study in Manitoba, Canada. *J Clin Psychiatry* 2014; 75: 154–161.
3. Laursen TM, Nordentoft M and Mortensen PB. Excess early mortality in schizophrenia. *Annu Rev Clin Psychol* 2014; 10: 425–448.
4. Wilkowska A, Kujawska-Danecka H and Hajduk A. Risk and prophylaxis of venous thromboembolism in hospitalized psychiatric patients: a review. *Psychiatr Pol* 2018; 52: 421–435.
5. Azad MC, Shoesmith WD, Al Mamun M, *et al*. Cardiovascular diseases among patients with schizophrenia. *Asian J Psychiatr* 2016; 19: 28–36.
6. Arasteh O, Nomani H, Baharara H, *et al*. Antipsychotic drugs and risk of developing venous thromboembolism and pulmonary embolism: a systematic review and meta-analysis. *Curr Vasc Pharmacol* 2020; 18: 632–643.
7. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007; 44: 62–69.
8. Jönsson AK, Spigset O and Hägg S. Venous thromboembolism in recipients of antipsychotics: incidence, mechanisms and management. *CNS drugs* 2012; 26: 649–662.
9. Hsu WY, Lane HY, Lin CL, *et al*. A population-based cohort study on deep vein thrombosis and pulmonary embolism among schizophrenia patients. *Schizophr Res* 2015; 162: 248–252.
10. Chow V, Reddel C, Pennings G, *et al*. Global hypercoagulability in patients with schizophrenia receiving long-term antipsychotic therapy. *Schizophr Res* 2015; 162: 175–182.
11. Pallares Vela E, Dave P and Cancarevic I. Clozapine-related thromboembolic events. *Cureus* 2021; 13: e16883.
12. Hoirisch-Clapauch S, Amaral OB, Mezzasalma MA, *et al*. Dysfunction in the coagulation system and schizophrenia. *Transl Psychiatry* 2016; 6: e704.
13. Masopust J, Malý R, Andrýs C, *et al*. Markers of thrombogenesis are activated in unmedicated patients with acute psychosis: a matched case control study. *BMC psychiatry* 2011; 11: 2.
14. Docx L, Sabbe B, Fransen E, *et al*. Longitudinal evaluation of the psychomotor syndrome in schizophrenia. *J Neuropsychiatry Clin Neurosci* 2014; 26: 359–368.
15. Rosebush PI, Hildebrand AM, Furlong BG, *et al*. Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. *J Clin Psychiatry* 1990; 51: 357–362.
16. Bresee LC, Majumdar SR, Patten SB, *et al*. Prevalence of cardiovascular risk factors and disease in people with schizophrenia: a population-based study. *Schizophr Res* 2010; 117: 75–82.
17. Osborn DP, Nazareth I and King MB. Physical activity, dietary habits and coronary heart disease risk factor knowledge amongst people with severe mental illness: a cross sectional comparative study

- in primary care. *Soc Psychiatry Psychiatr Epidemiol* 2007; 42: 787–793.
18. Elmi S, Sahu G, Malavade K, *et al.* Role of tissue plasminogen activator and plasminogen activator inhibitor as potential biomarkers in psychosis. *Asian J Psychiatr* 2019; 43:105–110.
 19. Dawson S and Henney A. The status of PAI-1 as a risk factor for arterial and thrombotic disease: a review. *Atherosclerosis* 1992; 95: 105–117.
 20. Iwata Y, Suzuki K, Nakamura K, *et al.* Increased levels of serum soluble L-selectin in unmedicated patients with schizophrenia. *Schizophr Res* 2007; 89: 154–160.
 21. Carville DG, Dimitrijevic N, Walsh M, *et al.* Thrombus precursor protein (TpP): marker of thrombosis early in the pathogenesis of myocardial infarction. *Clin Chem* 1996; 42: 1537–1541.
 22. LaCapra S, Arkel YS, Ku DH, *et al.* The use of thrombus precursor protein, D-dimer, prothrombin fragment 1.2, and thrombin antithrombin in the exclusion of proximal deep vein thrombosis and pulmonary embolism. *Blood Coagul Fibrinolysis* 2000; 11: 371–377.
 23. Lippi G, Cervellin G, Franchini M, *et al.* Biochemical markers for the diagnosis of venous thromboembolism: the past, present and future. *J Thromb Thrombolysis* 2010; 30: 459–471.
 24. Barbui C, Conti V and Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. *Drug Saf* 2014; 37: 79–90.
 25. Kleijer BC, Heerdink ER, Egberts TC, *et al.* Antipsychotic drug use and the risk of venous thromboembolism in elderly patients. *J Clin Psychopharmacol* 2010; 30: 526–530.
 26. Thorup M and Fog R. Clozapine treatment of schizophrenic patients: plasma concentration and coagulation factors. *Acta Psychiatr Scand* 1977; 55: 123–126.
 27. Sadler JE. Biochemistry and genetics of von Willebrand factor. *Annu Rev Biochem* 1998; 67: 395–424.
 28. Gravanis I and Tsirka SE. Tissue-type plasminogen activator as a therapeutic target in stroke. *Expert Opin Ther Targets* 2008; 12: 159–170.
 29. Brusov OS, Simashkova NV, Karpova NS, *et al.* Thrombodynamic parameters of hypercoagulation of blood in children with childhood autism and schizophrenia. *Zh Nevrol Psikhiatr Im S S Korsakova* 2019; 119: 59–63.
 30. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull* 2018; 44: 973–982.
 31. Prestwood TR, Asgariroozbehani R, Wu S, *et al.* Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia. *Behav Brain Res* 2021; 402: 113101.
 32. Monteiro R and Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm* 2010; 2010: 289645.
 33. Sugino H, Futamura T, Mitsumoto Y, *et al.* Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; 33: 303–307.
 34. Stapel B, Sieve I, Falk CS, *et al.* Second generation atypical antipsychotics olanzapine and aripiprazole reduce expression and secretion of inflammatory cytokines in human immune cells. *J Psychiatr Res* 2018; 105: 95–102.
 35. Szuster-Ciesielska A, Słotwińska M, Stachura A, *et al.* Neuroleptics modulate cytokine and reactive oxygen species production in blood leukocytes of healthy volunteers. *Arch Immunol Ther Exp (Warsz)* 2004; 52: 59–67.
 36. Caruso G, Grasso M, Fidilio A, *et al.* Antioxidant properties of second-generation antipsychotics: focus on microglia. *Pharmaceuticals (Basel)* 2020; 13: 457.
 37. Na KS, Kim WH, Jung HY, *et al.* Relationship between inflammation and metabolic syndrome following treatment with paliperidone for schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; 39: 295–300.
 38. Hagi K, Nosaka T, Dickinson D, *et al.* Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry* 2021; 78: 510–518.
 39. Xu H and Zhuang X. Atypical antipsychotics-induced metabolic syndrome and nonalcoholic fatty liver disease: a critical review. *Neuropsychiatr Dis Treat* 2019; 15: 2087–2099.
 40. Dai L, Zuo Q, Chen F, *et al.* The association and influencing factors between antipsychotics exposure and the risk of VTE and PE: a systematic review and meta-analysis. *Curr Drug Targets* 2020; 21: 930–942.

41. Steffen LM, Cushman M, Peacock JM, *et al.* Metabolic syndrome and risk of venous thromboembolism: longitudinal investigation of thromboembolism etiology. *J Thromb Haemost* 2009; 7: 746–751.
42. Lohr JB and Flynn K. Smoking and schizophrenia. *Schizophr Res* 1992; 8: 93–102.
43. Mak YW, Loke AY and Chiang VCL. Co-occurrence of schizophrenia and smoking: a qualitative study. *Hong Kong Med J* 2019; 25: 21–27.
44. Sagud M, Mihaljević-Peles A, Mück-Seler D, *et al.* Smoking and schizophrenia. *Psychiatr Danub* 2009; 21: 371–375.
45. Cheng YJ, Liu ZH, Yao FJ, *et al.* Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Med* 2013; 10: e1001515.
46. Lally J, Spaducci G, Gardner-Sood P, *et al.* Tobacco smoking and nicotine dependence in first episode and established psychosis. *Asian J Psychiatr* 2019; 43: 125–131.

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