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RESEARCH ARTICLE

Antioxidant Enzymes and Weight Gain in Drug-naive First-episode Schizophrenia Patients Treated with Risperidone for 12 Weeks: A Prospective Longitudinal Study

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Abstract: ***Background*:** Oxidative stress plays an important role in weight gain induced by antipsychotics in schizophrenia (SCZ). However, little is known about how antioxidant enzymes are involved in weight gain caused by risperidone monotherapy in antipsychotics-naïve first-episode (ANFE) patients with SCZ. Therefore, the main purpose of this study was to investigate the effects of risperidone on several antioxidant enzymes in patients with ANFE SCZ and the relationship between weight gain and changes in antioxidant enzyme activities.

***Objective*:** The activities of plasma superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as the levels of malondialdehyde (MDA) were measured in 225 ANFE patients and 125 healthy controls.

***Methods*:** Patients were treated with risperidone monotherapy for 12 weeks. Clinical symptoms, antioxidant enzyme activities, and MDA levels were measured at baseline and during follow-up.

***Results*:** Compared with healthy controls, the patients showed higher activities of SOD and CAT but lower MDA levels and GPx activity. At baseline, the CAT activity was associated with body weight or BMI. Further, based on a 7% weight increase from baseline to follow-up, we found 75 patients in the weight gain (WG) group and 150 patients in the non-WG group. Comparing SOD, CAT, GPx activities and MDA levels between the WG group and the non-WG group at baseline and during the 12-week follow-up, it was found that after treatment, the SOD activity in the WG group increased while the MDA level decreased in the non-WG group. Moreover, baseline SOD and GPx activities were predictors of weight gain at 12-week follow-up.

***Conclusion*:** These results suggest that the antioxidant defense system may have predictive value for the weight gain of ANFE SCZ patients after risperidone treatment.

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1. INTRODUCTION

Schizophrenia (SCZ) is a serious mental disorder with a worldwide prevalence of approximately 1.3% [1]. Antipsychotics are the main treatment to relieve symptoms and significantly improve the quality of life of SCZ patients. However, antipsychotics can cause serious adverse reactions, such as weight gain, obesity, and a higher risk of metabolic syndrome [2, 3]. The weight gain induced by antipsychotics varies substantially among individuals in ways that cannot be fully explained by differences in drug action, exercise, diet, and other factors. Currently, after antipsychotics treatment, some biological systems and biochemical pathways appear to affect weight gain [4, 5].

The increase in oxidative stress (OxS) is frequently accompanied by a decrease in antioxidant capacity and an increase in the production of reactive oxygen species [6]. Studies on the animal models of SCZ have shown that reactive oxygen species may be produced by enhanced metabolism of dopamine, which is converted to hydrogen peroxide through auto-oxidation or monoamine oxidase [7]. Hydrogen peroxide induces OxS on cells, which may be neurotoxic [8]. Antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) can convert free radicals and reactive oxygen species into water or

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oxygen, thereby preventing damage [9]. Mechanistically, however, these enzymes differ in the way they produce these byproducts and the stages in which they react with the free radical pathways [10]. SOD is a critical enzyme that catalyzes the conversion of superoxide radicals into molecular oxygen and hydrogen peroxide [11, 12]. GPx is responsible for the further conversion of hydrogen peroxide into oxygen and water [10]. CAT is one of the main enzymes for the antioxidant mechanisms and decomposes hydrogen peroxide into water and oxygen. In short, the above 3 critical antioxidant enzymes in the antioxidant defense system (AODS) have synergistic effects at different stages of the free radical scavenging pathway. Although we can obtain information by detecting 3 antioxidant enzyme activities, malondialdehyde (MDA), the end product of lipid peroxidation, is a direct marker of OxS [13].

Accumulating clinical studies support that antipsychotic drug treatment induces OxS markers and participates in adverse effects in SCZ patients, such as weight gain and obesity [14-17]. Previous studies have shown that the activities of the key antioxidant enzymes in AODS are undermined, and the pro-oxidative status is enhanced in obese subjects [18-21]. It is worth noting that a few studies have found that abnormal OxS markers are associated with weight gain and obesity in SCZ patients. For example, fat accumulation and obesity have been shown to be related to excessive production of reactive oxygen species and activation of AODS [22, 23].

Our recent study in chronic SCZ patients treated with antipsychotics found that the level of MDA in the group with high BMI was significantly higher, and the MDA level was positively correlated with BMI [24]. Also, the results from other studies have revealed a close relationship between obesity and free radical-mediated OxS markers [25-26] and a reverse relationship between BMI and total antioxidant capacity in healthy men and women [23]. In SCZ, it has also been found that obesity caused by antipsychotic drug treatment is associated with changes in OxS markers. Oxidative damage caused by antipsychotic drugs may lead to the development of obesity [15-17]. Taken together, these studies collectively support the role of OxS in the pathophysiology of obesity-related to antipsychotic treatment, suggesting that the abnormal antioxidants in conjunction with oxidative stress may serve as future biomarkers for weight gain induced by antipsychotic drugs in first-episode drug naïve patients (FEDN) with SCZ.

Risperidone is the most frequently prescribed second-generation antipsychotic in the treatment of SCZ, showing that risperidone is the less atypical or the most typical among the atypical antipsychotics [27, 28]. Previous studies have shown that risperidone may increase the production of free radicals by blocking dopamine receptors, increasing dopamine metabolism, and affecting dopamine circulation [17, 29]. However, whether risperidone treatment may significantly change the activities of antioxidant enzymes in SCZ patients and further lead to weight gain at follow-up is still inconsistent [30-33]. Based on these previous studies on OxS markers and weight gain induced by antipsychotics, we proposed that risperidone treatment may cause changes in antioxidant enzymes and further participate in the weight gain of SCZ patients. This study was intended to explore (1) whether the antioxidant enzyme activities at baseline were associated with BMI or weight in patients with ANFE SCZ; (2) whether risperidone treatment affected antioxidant enzyme activities; and (3) whether there was a relationship between weight gain induced by risperidone treatment and baseline or changes in antioxidant enzyme activities during treatment.

2. SUBJECTS AND METHODS

2.1. Subjects

SCZ patients were recruited from Beijing Huilongguan Hospital and Henan Zhumadian Hospital according to the previously published criteria for the first episode and drug naïve patients [34]. The inclusion criteria included: SCZ diagnosis with the Chinese version of SCID as assessed by six experienced psychiatrists [35]; belonging to the Chinese Han population; aged between 16 and 45 years; disease duration of fewer than 60 months; no previous treatment with antipsychotics or cumulative antipsychotic exposure less than 14 days. The exclusion criteria were as follows: any other major Axis I disorders; systemic diseases with oxidative stress etiology; organic brain disease, brain injury or other systemic diseases; pregnant or lactating women; drinking alcohol; substance abuse or dependence other than tobacco. We also obtained detailed medical conditions from each patient to rule out medical abnormalities.

Since admission, all patients received dietetically balanced meals provided by the canteen of the hospital and had one hour of physical exercise every day. All patients had similar foods, and they occasionally received gifts (usually fruits and snacks) as supplements.

One hundred and twenty-five unrelated healthy subjects were also recruited from the local community, and none of them had personal or family history of psychiatric disorder confirmed by clinical psychiatrists using SCID. We also ruled out the control subjects who received mood-stabilizing drugs, anti-anxiety drugs, antidepressants, or antipsychotics. All patients and healthy controls were Han Chinese.

The Institutional Review Board (IRB) of Beijing Huilongguan Hospital approved this protocol. Written informed consent was obtained from all subjects prior to the performance of any study-related procedures.

2.2. Treatment and Measurement

SCZ patients entered a 12-week clinical treatment with risperidone. Benzodiazepines could be used for patients with sleep disorders, and anticholinergic drugs could be used for patients with extrapyramidal side effects. This study was conducted in two hospitals in China.

At baseline and the end of 12 weeks, body weight was measured with an electronic scale calibrated to ±0.1 kg following overnight fasting. After emptying their pockets, the subjects wore light clothes without shoes, and measured their weight. The height was collected when the subjects were barefoot and upright. The height was measured to the nearest millimeter. The same scale and height measurement device were used during the study. BMI was calculated by weight over squared height, kg/m^2. All measurements for each patient were repeated twice to obtain an average value. If the patient's weight gain exceeded 7% of the baseline weight, we

defined the patient as the weight gain (WG) group and the other patients as the non-weight gain (non-WG) group [36].

2.3. Assessments of Psychotic Symptoms of the Patients

Four experienced clinical psychiatrists assessed the patients' psychiatric symptoms through PANSS after a training course [37]. Repeated assessment analysis showed that the inter-observer correlation coefficient of the PANSS total score remained >0.8. We assessed the psychotic symptoms of the patients at baseline and follow-up.

2.4. Determination of OxS Markers in the Patients and Controls

As described in previous literature [14], the activities of antioxidant enzymes (GPx, CAT, and SOD) and MDA levels were detected by spectrophotometer. Antioxidant enzyme activities were expressed in units of plasma per milliliter (U/ml). Total SOD activities were assayed using a standard assay method involving the spectrophotometric determination of the inhibition of superoxide-induced formation of nitrite from hydroxylamine. Xanthine-xanthine oxidase provides superoxide sources. One unit is defined as the amount of SOD that inhibits 50% of the nitrite formation under the assay conditions. CAT activity was determined based on the decomposition of hydrogen peroxide by CAT, which catalyzes the transformation of hydrogen peroxide to water and oxygen. The activity was determined by monitoring the decreased absorbance spectrophotometrically at 240 nm due to the degradation of hydrogen peroxide. One unit of CAT is defined as the amount of enzyme that decomposes 1 μmol H_2O_2/min under specific conditions. Determination of GPx activity was conducted based on a method that the enzymatic reaction was initiated by adding H_2O_2 to the reaction mixture containing reduced glutathione, reduced nicotinamide adenine dinucleotidephosphate (NADPH), and glutathione reductase. The change in the absorbance of the 340 nm was monitored by a spectrophotometer. One unit of GPx is defined as micromoles of NADPH oxidized per minute. The activity was given in units per liter plasma volume. The MDA levels were measured by the thiobarbituric acid (TBA) method. MDA values were calculated using the extinction coefficient of MDA–thiobarbituric acid complex at 532 nm, which were expressed in nmol/ml.

2.5. Statistical Analysis

Analysis of variance (ANOVA) or X^2 tests was performed to compare demographics, clinical characteristics, weight, and BMI between healthy controls and patients at baseline. We conducted a multiple analysis of covariance (MANCOVA) to compare the antioxidant enzyme activities between patients and healthy controls. The covariates in the MANCOVA analysis included sex, smoking status, age, and body mass index (BMI). Bonferroni corrections were used to adjust multiple comparisons. Then, the Pearson product-moment correlation analysis was performed to examine the relationship between antioxidant enzymes and bodyweight or BMI at baseline.

293 patients received risperidone treatment for 12 weeks, and 211 patients completed the study. The last observation carried forward (LOCF) analysis was performed for patients who dropped out after the second month. Finally, 225 patients were analyzed by using intention-to-treat (ITT) analysis. 75 patients were classified into the WG group, and 150 patients were classified into the non-WG group. In the follow-up analysis, we investigated whether there was a significant difference in antioxidant enzyme activities between the WG group and the non-WG group after 12 weeks of risperidone monotherapy. We performed a 2 × 2 (group by time point) repeated measure MANOVA analysis (RM MANOVA), with antioxidant enzyme activities as the result measurement. After the RM MANOVA test, a significant multivariate omnibus test was performed, and then the univariate effect was examined. The effects of time, group, and the interaction between time and group were examined. If the group × time interaction was significant, an analysis of covariance (ANCOVA) with baseline antioxidant enzyme activity as a covariate was then used to analyze the differences between groups at 12-week follow-up.

After controlling for age, sex, baseline BMI and education multiple linear regression analysis with weight gain as an independent variable was also performed to detect whether the baseline antioxidant enzyme activity or the change of each antioxidant enzyme could predict weight gain caused by risperidone.

We used SPSS version 22.0 for all statistical analyses, and the statistical significance was set to $p<0.05$.

3. RESULTS

3.1. Baseline Comparison of Subject Characteristics and OxS Markers

The demographic data of SCZ patients and healthy controls are shown in Table **1**. There were significant differences in education and BMI between patients and controls ($p<0.05$). Compared with controls, SCZ patients showed lower MDA levels and GPx activity but higher SOD and CAT activities (all $p<0.05$ after Bonferroni corrections).

Moreover, partial correlation analysis showed that the baseline body weight or BMI was associated with CAT activity (weight: r=0.15, p=0.039; BMI: r=0.18, p=0.014) in SCZ patients. When the patients were divided into the WG group (n=75) and non-WG group (n=150), we found that there were no significant differences in several antioxidant enzyme activities between the two groups (all $p>0.05$). However, we found that the WG group had younger age, lower baseline BMI and shorter duration of illness than the non-WG group (all $p<0.05$).

3.2. Risperidone Treatment, Weight Gain, and Antioxidant Enzyme Activity

At baseline, there were significant differences in age, disease duration, weight, and BMI between the WG group and the non-WG group (all $p<0.05$), which were controlled in the following analysis. After 12 weeks of risperidone treatment, the patient's body weight was significantly higher than the baseline ($p<0.01$, after Bonferroni corrections) (Table **2**).

To test whether 12-week risperidone treatment altered the antioxidant enzyme activities and whether there were differences between the WG group and the non-WG group, a repeated-measures MANOVA was performed with antioxidant enzyme activities as the result index. The results revealed

Table 1. Demographic characteristics and clinical data in healthy controls and antipsychotics-naive first episode (ANFE) patients with schizophrenia (SCZ) at baseline.

Variable	Patients (n=225)	Controls (n=125)	p-value	WG (n=75)	Non-WG (n=150)	F or χ^2 (p-value)
Gender(M/F)	124/101	77/48	0.26	46/29	78/72	1.8(0.20)
Age (ys)	27.9 ± 9.3	27.6 ± 7.0	0.90	26.0±8.2	28.8±9.7	4.7(0.03)
Education (ys)	9.3 ± 3.9	10.3 ± 3.1	0.01	9.4±3.7	9.3±4.0	0.1(0.73)
Tobacco use (smoker, %)	64(28.4)	44(35.2)	0.23	22(29.3)	42(28.0)	0.04(0.88)
BMI (kg/m^2)	21.4 ± 3.5	23.5 ± 4.1	0.001	19.5±2.1	22.3±3.6	38.4(<0.001)
Onset age (ys)	26.2 ± 9.2	-	-	24.9±7.8	26.8±9.8	2.1(0.15)
Duration of illness (ms)	20.3±19.4	-	-	17.3±11.2	23.2±18.1	6.6(0.01)

Abbreviations: *ys* years; *ms* months; *BMI* Body mass index; *WC* waist circumference; *HC* hip circumference; *WG* weight gain; *non-WG* non-weight gain.

Table 2. Weight and psychotic symptoms in ANFE SCZ patients after treatment with 12 weeks of risperidone (Mean ± SD).

Variable	Baseline	Post Treatment	Change in Score at Endpoint [Mean, (95%CI)]	t (p)
Weight(kg)	59.4 ± 11.7	62.0 ± 11.2	2.6 (2.11, 3.08)	10.5(<0.001)
BMI(kg/m^2)	21.4 ± 3.5	22.4 ± 3.2	1.0 (0.80, 1.14)	10.9(<0.001)
PANSS total score	76.3 ± 17.5	51.1 ± 12.9	-25.2 (-27.69, -22.73)	-20.1(<0.001)
P subscore	22.2 ± 6.4	11.8 ± 4.5	-10.3 (-11.19, -9.45)	-15.8(<0.001)
N subscore	18.7 ± 6.9	14.3 ± 5.7	-4.4 (-5.25, -3.58)	-10.4(<0.001)
G subscore	35.7 ± 9.7	25.0 ± 6.0	-10.7 (-11.94, -9.41)	-16.6(<0.001)

Abbreviations: *PANSS* Positive and Negative Syndrome Scale total and subscales; *P* positive symptom; *N* negative symptom; *G* general psychopathology.

Table 3. Baseline and changes in antioxidant enzyme activities and MDA levels in WG group and non-WG group after 12-week treatment with risperidone.

Variable	Baseline	F (p)	Change in Markers at Endpoint	F (p)
MDA (nmol/ml) (n=187)	-	1.2(0.37)	-	3.3(0.06)*
WG	2.3 ± 1.6	-	-0.45 ± 1.5	-
Non-WG	2.1 ± 1.3	-	-0.09 ± 1.2	-
SOD (U/ml) (n=216)	-	5.1(0.02)	-	12.3(0.001)*
WG	72.9 ± 9.1	-	4.4 ± 12.4	-
Non-WG	76.1 ± 10.1	-	-0.6 ± 8.5	-
GPx (U/ml) (n=205)	-	0.6(0.44)	-	2.9(0.09)
WG	55.1 ± 18.2	-	-8.3 ± 18.5	-
Non-WG	57.3 ± 18.7	-	-3.7 ± 18.5	-
CAT (U/ml) (n=193)	-	1.2(0.28)	-	1.1(0.30)
WG	0.33 ± 0.3	-	-0.05 ± 0.3	-
Non-WG	0.39 ± 0.4	-	0.12 ± 0.5	-

Abbreviations: *MDA* malondialdehyde; *SOD* superoxide dismutase; *GPx* glutathione peroxidase; *CAT* Catalase; *WG* weight gain.

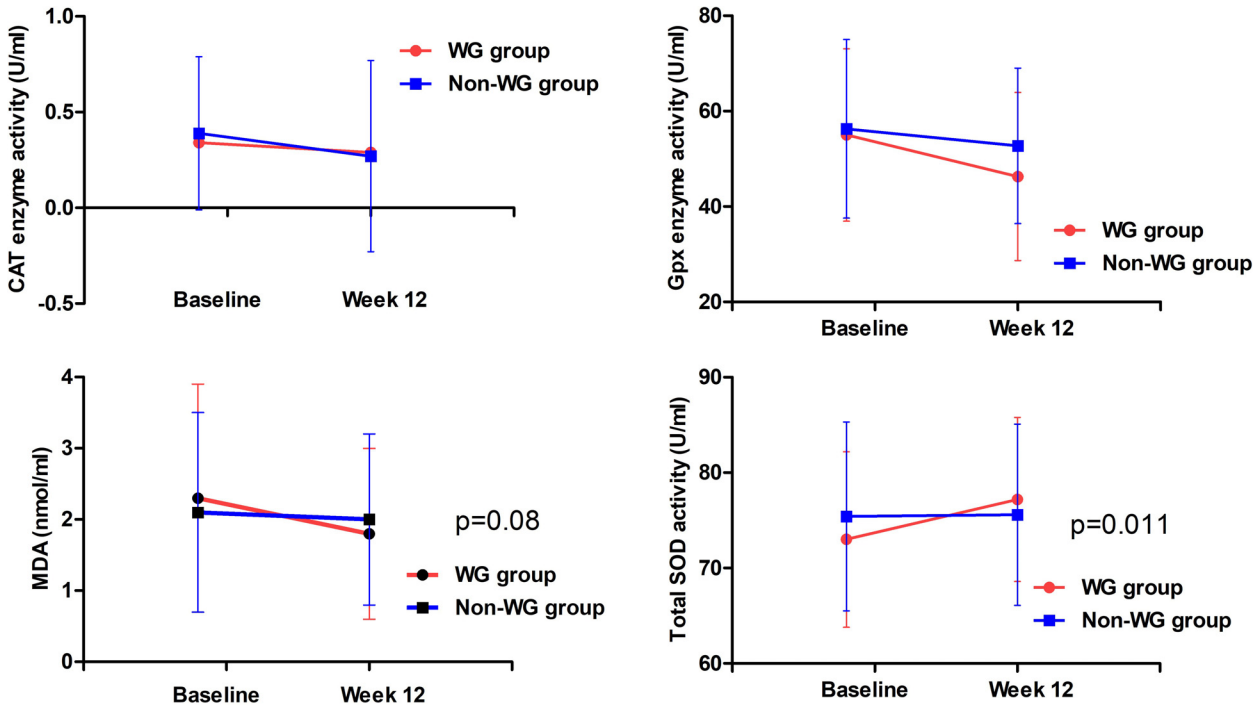

Fig. (1). Levels of MDA, activities of GPx, SOD and CAT enzyme were altered after risperidone monotherapy for 12 weeks in WG group and non-WG group.

that there was a significant interaction effect of group × time (Wilks' lambd`a F = 2.8, p = 0.031), without main effects of group and time (all p>0.05). Univariate analysis showed that there was a significant interaction of group × time (F=9.6, p=0.002), but there was no group and time main effect (all p>0.05).

As shown in Fig. (**1**) and Table **3**, we found that from baseline to week 12 in the WG group, risperidone treatment increased SOD activity (t=-2.4, p=0.03) but did not show any effect on SOD activity in the non-WG group (t=0.6, p=0.57).

For MDA levels, there was a trend towards statistical significance in the interactive effect of group × time (F=3.2, p=0.08), but there was no main effect of group and time (all p>0.05). Risperidone treatment significantly decreased the MDA levels in the WG group, but showed no effect on the MDA levels in the non-WG group. There were no significant main effects of group, time, and the interactive effect of group × time on CAT and GPx (all p>0.05).

3.3. Association between Antioxidant Enzyme Activities at Baseline and Weight Gain Induced by Risperidone Monotherapy for 12 Weeks

Multivariable linear regression was performed to investigate the relationship between baseline antioxidant enzyme activities and risperidone-induced weight gain. In the regression model, weight gain was an independent variable, while age, education, smoking, baseline BMI and baseline antioxidant enzyme activities were covariates. The results showed that the activities of SOD and GPx at baseline were predictors of the female patients gained weight after risperidone treatment (for SOD: β=-0.23, t=-2.3, p=0.025; for GPx: β=-0.24, t=-2.5, p=0.014) (Table **4**).

4. DISCUSSION

To our best knowledge, this is the first study to reveal that changes in the activities of several antioxidant enzymes were correlated with weight gain caused by risperidone treatment in ANFE patients with SCZ. In this study, it was found that the activities of SOD and CAT in patients with ANFE SCZ were higher than those in healthy control subjects, while the MDA levels and GPx activity were lower than those in healthy controls. These broad differences indicated that a major redox regulation remodeling had taken place in ANFE SCZ patients and was correlated with baseline body weight. In addition, risperidone treatment for 12 weeks had different regulatory effects on antioxidant enzymes in the WG group and non-WG group, especially on SOD activity and MDA level.

Consistent with previous studies conducted in ANFE patients, this study also showed extensive changes in the baseline antioxidant enzyme activities and MDA levels. The finding of abnormalities in the main antioxidant enzymes in ANFE patients indicates that the remodeling of the redox regulatory system occurs in the early stage of the disease. Several studies have consistently shown that both chronic patients and first-episode SCZ patients have higher OxS [14, 38]. The possible mechanism is that antioxidant enzymes are the main defense against OxS, which were produced to protect from free radical damage in SCZ. In addition, we found that the antioxidant enzyme of CAT was associated with body weight or BMI in the early stage of the disease, which is in line with previous studies of SCZ showing that activated antioxidant enzymes were correlated with abnormal metabolism of patients [39].

Table 4. Multivariable analysis of factors associated with weight gain after 12-week treatment.

Variables	β	95% CI	t	p value
Age (y)	-0.07	-0.09 to 0.04	-0.68	0.50
Education (y)	-0.22	-0.36 to -0.02	-2.28	0.03
Smoking status	-0.04	-2.85 to 1.88	-0.41	0.69
Baseline BMI (kg/m^2)	-0.19	-0.37 to 0.002	-1.96	0.05
SOD (U/ml)	-0.23	-0.12 to -0.008	-2.28	0.025
GPx (U/ml)	-0.24	-0.37 to 0.02	-2.51	0.014

Interestingly, we found that ANFE patients with low baseline BMI, younger age, and shorter duration of illness had more weight gain after 12 weeks of treatment with risperidone. Our findings of a negative association between weight gain and baseline BMI, age, or duration of illness were in line with the results reported by other studies [40-43]. Although the exact mechanism remains unclear, higher appetite levels and binge-eating in ANFE patients after risperidone treatment may explain part of this phenomenon [43]. This study further demonstrated that after risperidone monotherapy, the SOD activity of the WG group increased and was also higher than that of the non-WG group. Our results indicate that the individual differences in redox regulation, especially the differences in antioxidant enzymes related to SOD activity, may be associated with the weight gain caused by risperidone in SCZ. Although we did not find any relationship between SOD and BMI at baseline, our longitudinal follow-up study demonstrated that the weight gain caused by risperidone monotherapy was associated with the increase in SOD. OxS is a hallmark of obesity, and accumulating studies have shown that the key enzymes of AODS (including SOD and GPx) in obesity are damaged [44], which is considered to be the first line of enzymatic scavenging of reactive oxygen species.

In our longitudinal study, the results showed that SOD activity of the WG group was not high in the initial stage of the disease but significantly increased after 12 weeks of treatment. SOD enzyme is the most important defense against OxS, which was increased to protect from free radical damage that spares reduced glutathione. Previous studies supported that antipsychotics enhanced the production of free radicals through drug metabolism and increased the conversion of catecholamine, resulting in an increase in antioxidant enzyme activities in SCZ patients after treatment [45, 46]. Patients in the WG group may have rapid dopamine metabolism and more OxS markers, which in turn activates the AODS system and leads to increased SOD activity as a compensation mechanism for OxS. Therefore, we found that the MDA level in the WG group was significantly diminished after treatment, but there was no difference in the non-WG group. Interestingly, our previous study has shown that there was a positive association between the decrease in PANSS scores and weight gain in ANFE patients after 12 weeks of risperidone treatment [47]. Unfortunately, we did not measure the plasma concentration of risperidone in patients, so we were unable to eliminate the effects of different plasma levels of risperidone. In short, our results suggest that after 12 weeks of risperidone treatment, weight gain involves the biologically active process of antioxidant enzyme activity. However, the SOD activity in this study was measured in plasma, and peripheral SOD may not reflect the SOD activity in the brain. Furthermore, some studies have proposed the opposite mechanism of enhanced production of free radicals induced by risperidone or other antipsychotics in the central nervous system. Therefore, the relationship between changes in SOD activity and other systems (*i.e.*, immune function, BDNF, and neurotransmission) and the weight gain caused by risperidone need further investigation.

A further finding of this study was that baseline SOD, and GPx activity were predictive markers of weight gain induced by risperidone monotherapy in female SCZ patients. These findings provide further evidence of the key role of SOD and GPx in the weight gain of female patients. The effect of risperidone treatment on SOD and GPx activities in SCZ patients has also been observed in several other studies [38, 48-52]. Impaired glutathione metabolism appears to play a key role in the progression of obesity. In high-fat, diet-fed rats with obesity and metabolic disorders showed significantly lower levels of antioxidant biomarkers, including SOD and GPx [53]. In type 2 diabetes mellitus (T2DM) associated with obesity, complex interactions between diabetes, obesity, and GPx or glutathione have been demonstrated [20, 54]. Abnormal glutathione metabolism has also been shown to play an overarching role in neurodegenerative diseases. A recent review has emphasized the critical role of peroxiredoxin 6 (PRDX6) in neuropsychiatric disorders, which has multiple functions of GPx activity and may provide novel insights for the development of effective pharmacological treatments and gene therapies [55]. In this study, we did not give an exact explanation why patients with low baseline SOD or low baseline GPx activity were more sensitive to weight gain after risperidone treatment. However, it is well known that GPx and SOD enzymes play a synergistic role in the antioxidant pathway, and GPx can further degrade SOD-catalyzed byproducts into oxygen and water [9, 56]. Because SOD and GPx constitute the first line of defense against OxS, the activities of SOD and GPx may be regulated in response to increased oxidative tone in the initial stage of SCZ as a compensatory mechanism [7, 57]. Thus, the abnormally regulated SOD and GPx activities in patients with first-episode SCZ suggest that OxS may occur in the initial phase of SCZ [39].

However, the source of the blood antioxidant enzymes remains unclear. So, it remains unknown whether those findings from blood may accurately mirror the changes in the

central nervous system. Substantial evidence exists that implicates the role of OxS and the blood-brain barrier (BBB) disruption in the pathogenesis of neurological diseases [58]. However, in the present study, we measured the activities of SOD, CAT, and GPx in plasma but not in the cerebral spinal fluid (CSF). Although we discussed the changes in the antioxidant enzyme activity and the relationship between antioxidant enzyme activities and weight gain primarily in the central nervous system, we have no direct evidence of whether plasma antioxidant enzyme activities may alter in a similar direction with the central nervous system.

This study has several limitations. First, only three enzymes in the antioxidant defense system were measured, which only reflects part of the antioxidant defense system. The antioxidant defense system is composed of enzymatic and non-enzymatic systems, cooperating sequentially to complete complex antioxidant defense functions. Therefore, this study only provides some insights into free radical-mediated dysfunction. Second, only one OxS biomarker was assessed, which is imprecise. We did not evaluate oxidative damage to proteins, lipids, and DNA, and other antioxidant barrier parameters. In particular, evaluation of glutathione metabolism is indicated. Third, more importantly, whether the peripheral antioxidant enzyme activities are correlated with their respective CNS counterparts is still uncertain.

CONCLUSION

In summary, this study shows that after 12 weeks of treatment, risperidone can regulate the patient's AODS system. The abnormal antioxidant enzyme activities in the peripheral blood of patients with ANFE SCZ were closely associated with weight gain. Compared with patients who have not gained weight, patients with weight gain showed higher SOD activity and lower MDA levels during 12-week follow-up. Interestingly, baseline plasma SOD and GPx activities may help predict risperidone-induced weight gain during the 12-week follow-up. Considering that the increase in SOD enzyme activity is correlated with weight gain caused by risperidone treatment, psychiatrists should pay more attention to patients with low SOD and GPx activity in clinical practice. Effective treatment through regulating OxS markers should be considered to reduce weight gain. However, due to the difficulty of establishing a clear correlation between blood oxidative markers and brain activity, this study should only be considered as preliminary.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board (IRB) of Beijing Huilongguan Hospital, China (Ethic No.: 2013-10). All subjects gave informed consent to participate in this study.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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