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Oxidative stress and schizophrenia: A comparative cross-sectional study of multiple oxidative markers in patients and their first-degree relatives

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Abstract

Objective: Schizophrenia (SCZ) is a chronic, disruptive mental disorder with unknown pathogenic mechanisms. Several studies evidenced that oxidative stress (OS) may be one of the causal factors to play a role in the pathophysiology of the disease. Our study aims to contribute to the SCZ research by investigating a possible relationship between the severity of illness (scored with "The Positive and Negative Syndrome Scale [PANSS]") and OS biomarkers in patients. We additionally assess the "first-degree-relatives (FDRs)" oxidative status with multiple parameters to test the idea of oxidative imbalance leads to disease progression as a genetical susceptibility factor.

Methods: This study included: 50 adult patients with SCZ, 50 unaffected FDRs, and 50 controls. OS biomarkers included myeloperoxidase (MPO), total oxidant status (TOS), total antioxidant status (TAS), total thiol (TT), native thiol (NT). Photometric methods were used to measure the parameters in the peripheral blood samples of participants. Disulphide (DS) and oxidative stress index (OSI) parameters were calculated.

Results: TOS, DS, OSI levels were significantly higher, and TAS, TT, NT levels were significantly lower in both SCZ and FDRs than controls. In the SCZ group, MPO activity was significantly higher compared with other groups. Results in this study did not provide a strong correlation between the PANSS and selected biomarkers. There was a slightly negative correlation between TT and PANSS in the SCZ group ($P = .041$, $r = -.297$).

Conclusion: OS biomarkers increased significantly in the peripheral blood of SCZ patients compared with other groups indicates the presence of OS in the aetiology of the disease. Mid-levels of oxidative markers found in FDRs imply that unaffected first-degree relatives have an increased risk for turning up to the clinical presentation stage.

Keypoints

- There is an oxidative imbalance and a low antioxidant capacity in both schizophrenia patients and their first-degree relatives compared with healthy individuals.
- If a family has a history of schizophrenia, high oxidative stress levels measured in unaffected first degree relatives may be considered as a risk factor for disease progression.

1 | INTRODUCTION

Schizophrenia (SCZ) is a neurodevelopmental disorder that begins in late adolescence-young adulthood and characterised by disruptions in perception, thought, emotion and behaviour. It remains a critical public health issue affecting more than 21 million people annually, which corresponds to 1% of the whole population. Although possible causes have not been understood clearly, researchers had identified genetic, environmental and vulnerability risk factors.[1] Contributing causes such as viral infections, low vitamin D exposure in the prenatal period, smoking, cannabis use, nutrition and childhood trauma are suggested to be these vulnerability factors.[2]

Among numerous efforts to describe molecular roots of SCZ, on top of the dopamine (DA) hypothesis, activated inflammatory pathways, specific genetic polymorphisms, neurodevelopmental and postnatal risk factors have been stated.[3] DA hypothesis has been the central idea suggesting the dysfunction in dopamine neurotransmission that is responsible for symptoms seen in SCZ, and the idea has led to therapeutical interventions to target the altered dopamine metabolism.[4] Activated immune-inflammatory response in the pathogenesis of SCZ is another landmark, as a variety of studies introduced the modulators of this response in the biospecimens of patients, and animal models proved that triggered immune reaction by disturbances such as pre-perinatal infections and other stress factors in the early period of neurodevelopment caused the lifelong increased immune response in individuals diagnosed with SCZ. Aberrant response by microglial cells to infections, trauma, environmental toxins and genetic dysfunction can lead to uncontrolled inflammation and so to neurodegeneration seen in SCZ patients.[5]

Increasing evidence suggests that oxidative stress (OS) can be considered as the common ground for disrupting factors in the disease development process. Oxidative-antioxidative imbalance is shown in SCZ patients as the elevated oxidative markers described in blood and cerebrospinal fluid of patients as well as decreased level of antioxidant defense component glutathione (GSH) in magnetic resonance spectroscopy (MRS) studies.[6,7] To identify the mechanisms referring to the impact of OS on disease aetiology, several studies put emphasis on the changes in the group of cells called "parvalbumin interneurons (PVIs)" that regulate cortical excitability and synaptic plasticity as well as cognitive functions.[8] PVIs are the last cells that appear during the developmental window, and these interneurons have been proved to be affected by OS.[9] Relatively slow development of these interneurons increases their vulnerability to environmental perturbations in their maturation period, as an animal study puts forth, repetitive activation of the IL-6/Nox2 pathway in PVIs alters the redox balance in favour of pro-oxidant state could explain the delayed effects observed in SCZ models.[10] The main dysfunction of PVI cells in SCZ pathophysiology is considered hypofunction of their N-methyl-D-aspartate receptors (NMDARs),[11] and it has been proved that NMDARs are essential for maintaining the normal oxidative status, a variety of mechanisms disrupting the function of these receptors have been found to led psychotic symptoms.[12]

What's known

- Schizophrenia (SCZ) has an inheritance of 80% and a lifetime risk of 1%, characterised by hallucinations, delusions, and cognitive deficits.
- Along with genetic and environmental factors, oxidative stress (OS) has been found to have a crucial role in SCZ.
- Before the onset, endophenotypic markers may manifest in healthy relatives at a higher rate compared with the general population.

What's new

- OS markers as total oxidant status (TOS), disulphide levels (DS), and oxidative stress index (OSI) were significantly higher, while total antioxidant status (TAS), total thiol (TT) and native thiol (NT) levels were lower in patients and their first-degree relatives compared with controls.
- Mid-levels of oxidative markers found in FDRs contribute to the literature by indicating the genetic background of the entity.

Antioxidant defense breakdowns as a cause of oxidative damage in SCZ patients involve glutathione (GSH), superoxide dismutase (SOD), and thiol metabolisms. GSH synthesis deficits have been reported in a group of SCZ patients.[13] Preclinical models show that GSH depletion triggers persistent psychotic symptoms during the postnatal period, and GSH deficit leads to NMDAR hypofunction as well as synaptic disruptions.[14] Recent clinical studies have found significantly lower levels of SOD and GSH along with higher levels of lipid oxidation markers in terms of oxidative imbalance by examining blood, cerebrospinal fluid (CSF) and post-mortem tissue.[15] Thiol-disulphide balance is another metabolic indicator of oxidative stress,[16] and in cases where oxidative stress increases, thiol-disulphide balance shifts in favour of disulphide. The level of thiol-containing compounds such as glutathione, cysteine, homocysteine and N-acetylcysteine is found altered in SCZ patient biospecimens, referring to the role of oxidative stress in aetiology.[17]

Other evidence for oxidative stress impact in schizophrenia may be explained by disruptions in cellular signalling pathways.[18] Also, DNA damage occurs as a target of H_2O_2 because of its large number of negatively charged ions binding cations under oxidative stress.

Eliciting the genetic basis of schizophrenia, several Genome-Wide Association Studies (GWAS) described multiple high-risk genes and among them, immune regulatory genes (namely, MHC) are found to be the most reliable evidence in the genesis of the disorder.[19] Many other genes associated with SCZ were associated with an antioxidant defense, such as Dysbindin[20] and the gene of GSH-synthesising enzyme, glutamate-cysteine ligase modifier (GCLM) subunit.[21] A meta-analysis has found the entity's estimated heritability around 80%.[22]

This study examines multiple oxidative markers in the peripheral blood of schizophrenia patients and their first-degree relatives (FDR), also searches for a correlation between OS parameters and the severity of illness in patients (determined by Positive and Negative Syndrome Scale [PANSS]). As a primary outcome, investigating the oxidative parameters in both SCZ patients and their first-degree relatives (FDR), our study analyses a possible endophenotypic role of FDRs for the first time. To mention, the secondary outcome of the study is the evaluation of the multiple OS markers at once. Since there are limited clinical studies including FDRs of schizophrenia patients, the current study fills the gap in the literature by testing if OS markers are elevated in FDRs, which would refer to the genetic background of the entity and confirm the aetiological role of OS.

2 | MATERIALS AND METHODS

The study design followed STROBE statements for cross-sectional studies, and the requirements in the checklist were fulfilled. The study complied with the Declaration of Helsinki and was approved by the clinical research ethics committee of Bezmialem Vakıf University (14/23—24.07.2019).

According to power analysis (at 80% power level), the cross-sectional study included 50 SCZ patients, 50 controls, and 50 patient relatives for the FDRs group.

From March 2017 to January 2018, the study involved patients who were diagnosed with schizophrenia in Bezmialem Vakıf University Medical Faculty Hospital. The schizophrenic patients had been diagnosed according to the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-VTR), and followed for at least three years in the psychiatry clinic of Bezmialem Vakıf University School of Medicine Hospital.[23] Psychiatrists who were blind to the clinical status and treatment conditions of patients were employed to assess the "PANSS" (recorded for only SCZ patients to reflect their psychopathological condition and severity of illness).

First-degree relatives and healthy controls were selected and interviewed in Bezmialem Vakıf University Medical Faculty Hospital at their visit. Each volunteer has been asked to provide written informed consent. First-degree relatives and healthy controls were assessed through a semi-structured psychiatric interview and a Social Cognition Scale, which assessed the domains: emotional processing, social perception, and attributional style in a Turkish population. No active psychopathology was detected in the psychiatric interview.

All participants were excluded from the study if they met one or more of the following criteria: chronic pathological diseases, alcohol/ cigarette/ substance abuse or dependence, cardiovascular diseases, diabetes mellitus, hepatic or renal failure, autoimmune diseases, active infection, active or chronic inflammatory diseases, obesity (greater than body mass index 30 kg/m^2) and treatment with anti-inflammatory, antioxidant or immunosuppressive medications. Sociodemographic data forms included comorbid medical diseases, alcohol/substance use, smoking status, family histories, job, education, body mass index (BMI) and were recorded for all volunteers. Participants were selected as having no comorbidities. Control and FDR groups were age and sex-matched with patients.

Blood was collected from all participants, and serums were analysed for the following parameters.

2.1 | Determination of total oxidant status

Serum TOS level was measured using a fully automatic photometric method developed by Erel.[24] The principle of the method, serum oxidants oxidise the ferrous ions of o-dianisidine into ferric ions. Ferric ions formed in an acidic environment as a result of this oxidation take a visible colour with xylenol orange. The resulting colour density is correlated with the level of oxidants in the serum. The standard of the method is H_2O_2. Results are given as μmol/L H_2O_2 equivalent. The sensitivity of the method is 2%.

2.2 | Determination of total antioxidant status

Serum TAS level is a fully automatic colorimetric method developed by Erel.[25] The principle of the method is based on measuring the amount of OH^- radical. The ferrous ion of o-diasidine reacts with H_2O_2 as the Fenton-type reaction to produce the OH^- radical, and colour change occurs because of o-diasidine. Serum antioxidants neutralise oxidants and prevent colour change. This method determines the antioxidant capacity against oxidative free radical reactions initiated by OH^-. The standard of this method is Trolox, which is an alpha-tocopherol analog. Results are given as mmol/L Trolox equivalent. The sensitivity of the method is 3%.

2.3 | Calculation of oxidative stress index

The serum OSI value is calculated by dividing the TOS value by the TAS value. OSI (arbitrary unit) = TOS (μmol H_2O_2 eq/L)/TAS (mmol Trolox eq/L).

2.4 | Determination of thiol/disulphide homeostasis (TDH)

New biomarkers of oxidative stress are thiol-disulphide homeostasis. In this method, total thiol, native thiol and disulphide levels are measured in serum developed by Erel and Neselioglu.[26] The principle of this method, dynamic disulphide bonds (-S-S-) in serum, is reduced to native thiol groups (-SH HS-) by sodium borohydride ($NaBH_4$). Total thiol level is measured photometrically using Ellman reagent. The disulphide level is calculated by subtracting the native

thiol level from the total thiol level and taking half of it. The unit of measurement for thiol-disulphide homeostasis is μmol/L.

2.5 | Activity of myeloperoxidase

The activity of MPO was determined by the method of Bradley et al,[27] which based on kinetic measurement of the formation rate of the colourful product of the oxidation of o-dianisidine with MPO in the presence of H_2O_2, at 460 nm. MPO activity was expressed as units per litre of serum (U/L).

2.6 | Statistical analysis

All statistical analyses were conducted with IBM SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA). All data are given as mean ± standard deviation. The distributions of the data were found with a single sample Kolmogorov-Smirnov test, and it was found to be a normal distribution. One-way analysis of variance (ANOVA) was used to determine whether there was a statistically significant difference between the groups. The Tukey test was applied for post hoc analysis. A Pearson correlation test was performed to evaluate the correlation between variables. A p-value less than 0.05 was accepted as statistically significant.

3 | RESULTS

3.1 | Socio-demographic data

A total of 50 patients with schizophrenia, 50 first-degree relatives, and 50 healthy controls have been listed. The socio-demographic variables of the study populations are presented in Table 1. There were no significant age, sex, smoking, and BMI differences between the schizophrenia, relative and control groups ($P > .05$). Marital status was found statistically different between the groups ($P < .05$). Job Status of the SCZ group has been observed at the lowest rate among the three groups ($P < .01$) (Table 1). The total PANSS value is obtained by summing all individual subscale scores of patients, and the average value can be seen in Table 1 (with the mean value of 67,6).

3.2 | Oxidative stress status

In our current study, we found that serum TOS and OSI levels have been found significantly higher ($P < .01$), and TAS levels were lower in the SCZ group than in the relatives and control groups ($P < .01$). Compared with the control group; TOS, OSI levels were significantly higher, and TAS levels were significantly lower in the relatives' group. As seen in Figure 1, MPO enzyme activity tended to be higher in the SCZ group compared with relatives and control groups ($P < .01$).

3.3 | Correlation analysis of PANSS and OS

The correlation between OS biomarkers and total PANSS score was investigated in the patient group. Results did not provide a significant correlation between PANSS and oxidative stress biomarkers. There was only a slight negative correlation between TT and total PANSS in the patients ($r = -.297$, $P = .041$).

3.4 | Thiol-disulphide homeostasis

Figure 2 reports thiol-disulphide homeostasis of SCZ, relatives and healthy controls. It has been found that plasma total and native thiol levels were highest in the controls, relatively lower in relatives, and lowest in the patients. There was a statistically significant difference

TABLE 1 Demographic characteristics of the present study

	Control	Relative	Schizophrenia	*P* value
Sex				
Female	19	25	20	NS
Male	31	25	30	NS
Age	38.9 ± 11.9	45.2 ± 15.4	42.4 ± 10.9	NS
Job				
Working	36 (%72)	26 (%52)	7 (%14)	<0.01
Not working	14 (%28)	24 (%48)	43 (%86)	<0.01
Single	21 (%42)	24 (%48)	41 (%82)	<0.01
Married	29 (%58)	26 (%52)	9 (%18)	<0.05
BMI	27 ± 5	26.5 ± 5.2	28.2 ± 5.9	NS
PANSS (total score)	—	—	67.6 ± 15.8	

Note: Data are presented as mean ± SD and number of volunteers.
Abbreviations: NS, not statistically significant; SD, standart deviation.

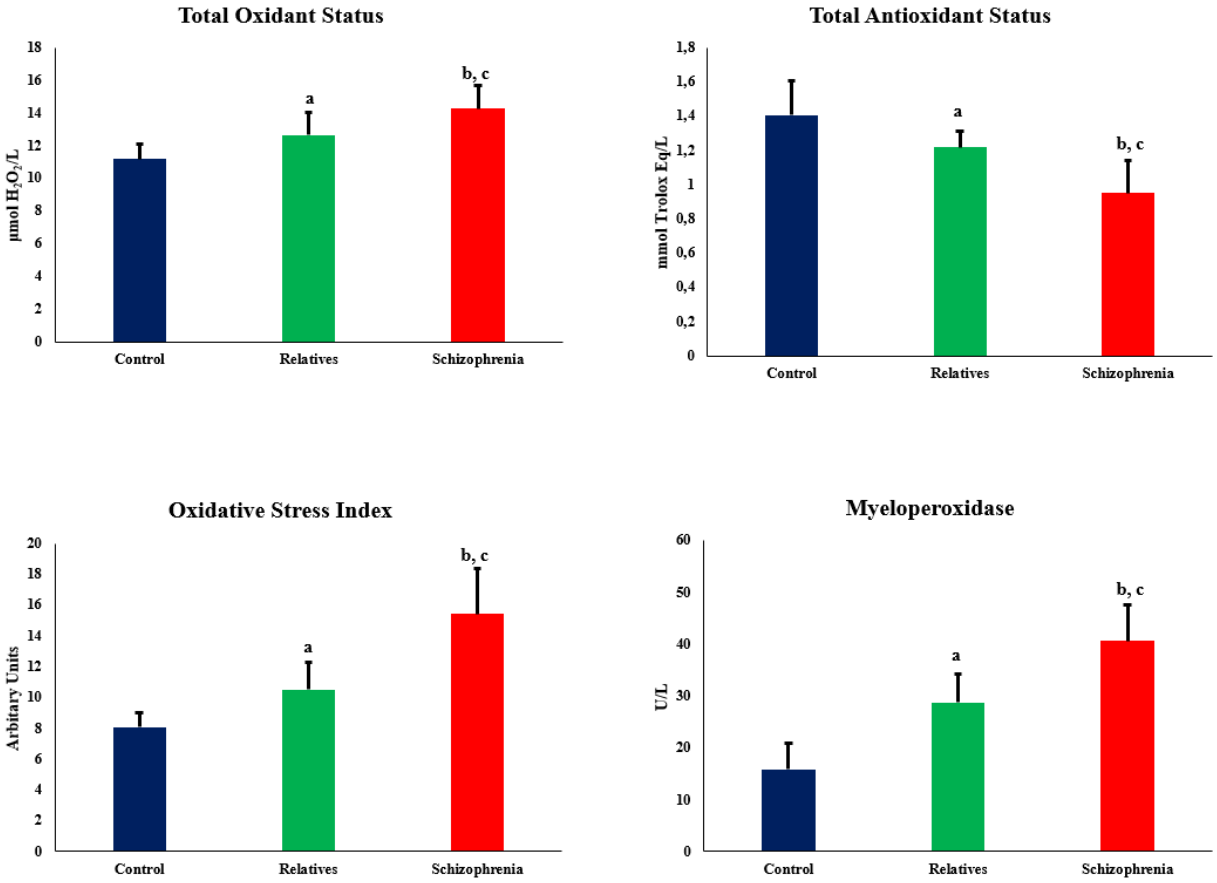

FIGURE 1 Changes of OS biomarker levels of all groups. [a]Statistically significant, compares control and relatives ($P < .05$). [b]Statistically significant, compares control and schizophrenia patients ($P < .05$). [c]Statistically significant, compares relatives and schizophrenia patients ($P < .05$)

in total and native thiol between the three groups ($P < .05$). Plasma thiol-disulphide levels were highest in the SCZ group, as shown in Figure 2. The thiol-disulphide level was relatively lower in the relatives' group than patients and was lowest in the control group. There was a statistically significant difference in thiol-disulphide levels between the three groups ($P < .05$) (Figure 2). Thiol-disulphide levels have not been found associated with the total PANSS in the patient group ($P > .05$).

4 | DISCUSSION

With the present study, we support the idea that OS markers might serve as a useful tool for risk estimation and diagnosis as well as placing new targets for intervention in schizophrenia patients. Our findings refer to the causal role of OS in disease progression by displaying significantly higher levels of oxidative markers in patients' blood while mid-levels in first-degree relatives (FDR). The unique data of mid-levels of multiple oxidative markers found in first-degree relatives contribute to the literature by indicating the genetic background of the entity. Higher levels of markers found in patient samples included the plasma total oxidant status (TOS) and oxidative stress index (OSI) levels with myeloperoxidase (MPO) enzyme activity. Patients had significantly lower values of total antioxidant status (TAS) and had the lowest level of plasma total and native thiol levels. FDR blood samples displayed mid-levels in between patients and controls for the whole marker profile (TOS, OSI, MPO, TAS, TT, and NT) except for the thiol-disulphide levels. There was no relationship between the oxidative markers and the severity of disease (assessed with PANSS score) in SCZ patients.

Growing knowledge in the relationship between SCZ and oxidative imbalance has led researchers to investigate if oxidative stress plays a role in the aetiology as a causal factor or it is an outcome of pathological processes.[28] Various studies investigating oxidant-antioxidant biomarkers in drug-naive first-episode psychosis (FEP) patients showed an increased pro-oxidative status (higher levels of homocysteine, IL-6, and TNF-α and lower levels of TAS, docosahexaenoic acid [DHA]) in patients compared with healthy controls.[29] Recent reports support the causal role of OS in psychosis development by displaying oxidative markers associated with the early stages of disease.[30] Our current results are consistent with a meta-analysis reporting lower TAS levels[31] and additionally show a significant decrease in both total and native thiol plasma levels in patients compared with controls. The meta-analysis has identified two marker groups as an indicator for disease progression; one is "state markers" such as total antioxidant status, plasma nitrite, red

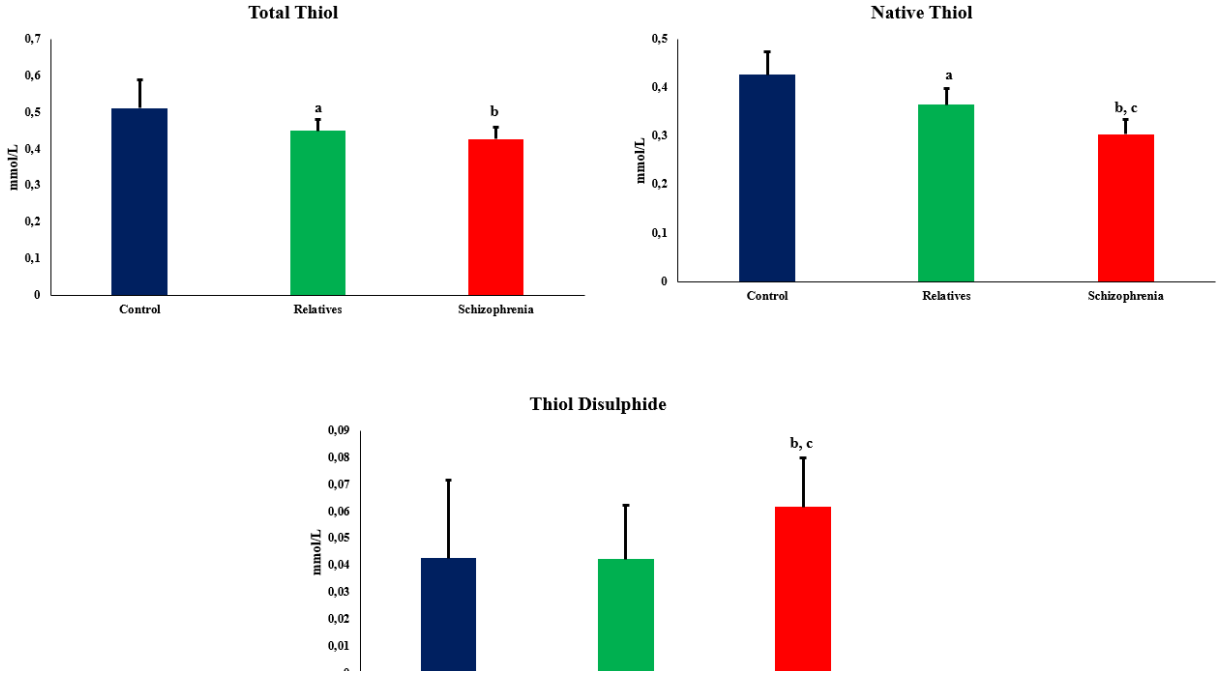

FIGURE 2 Changes of serum thiol-disulphide homeostasis biomarker levels of all groups. [a]Statistically significant, compares control and relatives ($P < .05$). [b]Statistically significant, compares control and schizophrenia patients ($P < .05$). [c]Statistically significant, compares relatives and schizophrenia patients ($P < .05$)

blood cell catalase, and the other group is "trait markers," including red blood cell catalase. It has been shown that by measuring the high clinical risk for psychosis (CHR) in individuals and then combining it with determined endophenotypes, psychosis progression might be predicted and intervened before its onset.[12] Further, a review gathering various studies highlights that oxidative status may help to identify specific endophenotypes of individuals at risk.[32] Our research showing the mid-level oxidative markers in patient relatives' blood supports the idea of risk prediction can be made before the onset of disease in individuals with higher oxidative parameters. This current finding imposes questions such as how we can benefit from patient relatives to identify some risky endophenotypes and how these phenotypes turn up to the clinical presentation stage, by which mechanisms, as well as how the gene by environmental interactions occur.

Studies involving first-degree relatives of schizophrenia patients have identified the increased oxidative stress and inflammation in these individuals.[33] Our study contributes to this data with raised levels of multiple oxidative parameters in FDRs compared with healthy controls. Still, further evidence is needed to fill the gap in the literature explaining irregular concentrations of the trait markers for SCZ apart from state ones.

Some contradictory results show that using oxidative status as a diagnostic clue identifying high-risk people, and a disease marker has not proved to be reliable, various studies found an insignificant difference for oxidative parameters between patients and controls.[7,34] A study claimed that PON-1 activity, together with oxidative-nitrosative stress (O&NS) biomarkers are not good indicators for chronic SCZ by showing no association between patients and controls.[35] This heterogeneity among results may be because of the different immunological, biochemical, endophenotypic profiles of individuals and the clinical heterogeneity of SCZ disease. Studies involving OS are open to interference from various factors such as psychological stress, comorbid diseases, and medication. Thus, investigating the causal role of OS in SCZ pathophysiology requires great attention, and this fact withdraws us to make strong assumptions about the temporal relationship between OS and the onset of the entity.[36]

To overcome difficulties faced in oxidative stress studies, human genome studies would offer to be a safe tool for eliciting the aetiology. GWAS studies helped researchers to determine candidate genes and revealed the polygenic nature of SCZ (identifying many common single-nucleotide polymorphisms (SNPs) over 150 genetic loci associated with synaptic function, neurodevelopment).[37] One study applied SNP scores obtained from a large-scale cognitive GWAS meta-analysis to SCZ case-control cohorts and addressed a genetic overlap between cognitive phenotypes and SCZ risk.[38] Similar molecular confirmations of the endophenotype hypothesis provided valuable insights to the understanding of why some individuals are more likely to develop SCZ in their late adolescence and early adulthood.[10,39-41] To obtain knowledge about complex processes beginning from cell level reaching to the behaviour, an interdisciplinary approach involving genetics and animal modelling is needed, and team science efforts would help to achieve this aim.[42]

Our clinical study contributes to literature comparing three groups (patients, their unaffected first-degree relatives, healthy controls) regarding individuals' oxidative status. It reports a significant difference in multiple oxidative markers in between these groups.

The unique finding of this work, patient relatives' mid-level values of oxidative markers, suggests that oxidative damage observed in individuals may result from a genetic vulnerability for SCZ. Taken together, this study enhances the oxidative stress research in SCZ and calls for future investigations to fill the gaps in the issue. Current findings of our work require replications with larger, well-designed studies excluding all intervening factors, and related socio-demographic and clinical variables should be analysed before offering a genuine association between OS and SCZ.

5 | CONCLUSIONS

The involvement of oxidative stress in SCZ pathophysiology is a widely accepted concept because of numerous findings on patient samples such as peripheral blood, CNS and post-mortem tissues. Still, which mechanisms lead to oxidative damage remains unclear, and arduous interdisciplinary work is required to enlighten the steps of disease progression. Our study contributes to the literature by analysing multiple oxidative parameters in peripheral blood of both patients and their unaffected first-degree relatives claiming that high levels of oxidative biomarkers would possibly be the indicator of SCZ progression in healthy individuals.

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DISCLOSURES

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

Based on a request, the data is available from the corresponding author.

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