Journal of Pharmaceutical Care
jpc.tums.ac.ir

Oxidative Stress and Bipolar Mood Disorder: An Important Yet Ambiguous Relationship

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Received: 2021-08-18, Revised: 2021-09-27, Accepted: 2021-10-04, Published: 2021-12-30

ARTICLE INFO

Article type:
Review article

COVID-19;
Bipolar Disorder;
Oxidative Stress;
Biomarkers

ABSTRACT

Bipolar disorder is a chronic psychological condition that disturbs many patients' lives around the world. The exact pathophysiology of bipolar disorder is yet unknown, but there are several hypotheses to explain this condition. One of the most challenging theories is the role of oxidative stress in the progression of bipolar disorder. Here, we conducted a narrative review to gather the studies that investigated the relationship between bipolar disorder and oxidative stress. We searched PubMed, Scopus, Web of science, and google scholar databases using the following keywords: "bipolar disorder," "oxidative stress," "oxidative markers," and "bipolar patients." A majority of studies showed that oxidative markers such as Thiobarbituric acid reactive substances are significantly higher in bipolar patients compared to healthy subjects. Based on the included articles, bipolar disorder is associated with oxidative stress. Nevertheless, further well-established Cohorts are required to support these results.

J Pharm Care 2021; 9(4): 195-208.

► **Please cite this paper as:**
Rahsepar S, Mohammadpour AH. Oxidative Stress and Bipolar Mood Disorder: An Important Yet Ambiguous Relationship. J Pharm Care 2021; 9(4): 195-208.

Introduction

Bipolar disorder (BD) is a lifetime mental disorder with a high impact on patients' quality of life and social activities. It is commonly known as episodes of mood instabilities and has several types. According to DSM-5 classification, Type I BD patients experience at least one mania episode, accompanied by depressive phases. For BD type 2 diagnosis, the patient presents a history of major depressive episodes and hypomania (at least one of each). This differentiation is essential for accurate pharmacotherapy and patient management (1).

The precise etiology of bipolar disorder is not clear; however, the most probable theory is the dual interaction of genetics and environmental factors. Based on the previous literature, BD is a neuroprogressive disease, and the patient's cognition and performance reduces over the years of mood swings, even during euthymic phases (1, 2). Several mechanisms are involved in this neuroprogression: the rise of dopamine and glutamate levels, inflammatory process, impairment of mitochondrial activity, and oxidative imbalance (3).

The term "oxidative stress" describes the imbalance between reactive oxygen species (ROS) production and the antioxidant system's ability to eliminate them. Either overproduction of ROS or a decrease in antioxidative agents can cause oxidative imbalance (3, 4).

During cellular respiration in mitochondria, some electrons escape the electron transfer chain and produce ROS. Evidence suggests that BD is associated with mitochondrial dysfunction, probably due to a dysregulation in mitochondrial genes (3,

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5). Besides, in BD patients, dopamine and glutamate levels increase, which have a high tendency to produce excess ROS (3). Another source of ROS production is neuroinflammation in BD patients. Oxidative stress and inflammation are highly interdependent and aggravate each other. Inflammatory processes produce free radicals, particularly due to microglia activation; therefore, oxidative stress increases (6, 7). On the other hand, clinical studies show some alterations in the antioxidant enzymes in BD patients (3).

There are various hypotheses to explain the effect of oxidative imbalance on physiological processes. An oxidative imbalance may lead to the oxidation of vital macromolecules, including lipids, proteins, DNA, and RNA. This damaging process can result in gene mutation, altered gene expression, protein denaturation, cell membrane destruction, and cell death (8).

Post-mortem samples of the prefrontal cortex show a high level of oxidation in synaptic proteins and myelin components. It can be implicated that oxidative stress disturbs signal transduction (9). A review by Gigante et al., Suggests that oxidative stress can trigger apoptosis and neuronal death. This hypothesis can explain the reason for brain atrophy and neuronal shrinking in BD patients (10). Another theory suggests that higher ROS production can lead to the oxidation of dopamine transporters. In a manic state, the dopamine level increases. An elevated level of dopamine leads to ROS generation, impairs dopamine transporters' function, and reduces dopamine re-uptake in synapses. Eventually, this vicious circle of dopamine accumulation may induce cytotoxicity and neuronal damage (11). Kapczinski et al., reported that oxidative stress might decrease the brain-derived neurotrophic factor (BDNF) level during manic episodes. Considering the role of BDNF in enhancing synaptic connectivity, this negative effect of oxidative stress can decrease synaptic function (12, 13).

According to a meta-analysis by Andreazza et al., 2008, lipid peroxidation markers (i.e., TBARS) are significantly higher in BD patients. Elevation of nitric oxide level, a major free radical and oxidative agent, is another indicator of higher oxidative activity. Although various clinical studies show changes in endogenous antioxidant enzymes (such as superoxide dismutase, Glutathione, and catalase), the results did not always match. While some studies showed higher activity of antioxidant systems, other studies reported a decrease in antioxidant enzymes (14). It is worth noticing that several variables can alter the level of oxidative stress in BD patients, such as somatic comorbidities, changes in circadian rhythm, substance abuse, mood-stabilizing medications, etc. (6, 15-17). Therefore, all these prevalent variables must be considered while investigating oxidative stress among BD patients.

Although there have been review studies regarding oxidative stress in bipolar disorder, they did not consider all the oxidative markers and focused on lipid peroxidation (14). In this article, we tried to consider many factors, both oxidative markers and antioxidant enzymes, to gain a better assessment of oxidative status. We also considered the role of medications in oxidative status alteration. However, we only did a narrative review which increases the risk of bias. Nevertheless, this paper can be an implication for further well-designed studies and systematic reviews.

Methods

In February 2021, we searched scientific databases including PubMed, Web of Science, Scopus, and google scholar with the following keywords (variously combined): "bipolar disorder," "oxidative stress," "oxidative markers," "bipolar patients." The search was limited to papers that were published after 2000. We chose the related articles based on their titles and abstracts. Our inclusion criteria were the papers that assessed the oxidative markers or antioxidant agents in bipolar patients with observational or interventional methods. On the other hand, non-human studies or in-vitro experiments were excluded. Accordingly, we read the full text of the articles and included those which were compatible with our criteria to enter the extraction process. We extracted the specific characteristics of patients and control subjects, measured oxidative marker and final results.

Results

After searching the databases using the pre-defined keywords, approximately 6200 articles were found. After applying a time limitation, we only considered the articles that got published in the time period of 2000 to 2020. We scanned the articles based on title and abstract and selected 96 papers that seemed potentially related to our subject. In the next step, we carefully evaluated these articles according to their full texts and included 48 articles in our review. We included the papers that evaluated oxidative stress markers in bipolar patients using observational or interventional designs. Case reports, animal studies, in-vitro studies, and review articles were excluded during the evaluation process.

Overall, this review includes 2447 bipolar patients and 1856 healthy controls. The bipolar patients had different mood episodes (mania, depression, and euthymia), which euthymia was the most frequent. Only three studies did not use a control group which lowers their value. Eighty-five percent of studies were observational and most frequently with cross-sectional design. The other fifteen percent of studies used an intervention like Lithium therapy with a before-after study design. None of the interventional studies were randomized, which reduces their quality. A majority of studies (87.5%) used blood samples from patients, while others used saliva, urine, and CSF. The included studies each used different markers to evaluate oxidative stress. The most frequent marker was superoxide dismutase. However, we summarized the included studies in Table1. Based on their attributes to provide a better way of comparison.

Table 1. Characteristics of the articles investigating oxidative stress in bipolar patients.

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Kuloglu et al.,2002 (18)	23/20	Blood	MDA, SOD, GPX	Not defined	• Exclusion criteria: substance abuse, severe somatic comorbidities, infection, severe obesity, tardive dyskinesia and epilepsy. • Not taking antioxidants.	• A significantly higher level of MDA and SOD. • No significant difference in GPX.
Savas et al.,2002(19)	44/21	Blood	NO	Mania	• Exclusion criteria: seizures, TBI, ECT therapy,chronic comorbidities, and addictions.	• A significantly higher level of NO.
Ranjekar et al.,2003(20)	10/31	Blood	CAT, SOD, GPX	Not defined	• Exclusion criteria: somatic comorbidities, dependency, seizure, TBI, severe malnourishment, or obesity. • Not taking high-dose supplementation.	• A significantly lower level of CAT. • No significant difference in SOD and GPX levels.
Ozcan et al.,2004(21)	18/21	Blood (baseline and after treatment)	CAT, NO, GPX, MDA, SOD	Mania or depression	• Exclusion criteria: recent addiction (besides nicotine), severe somatic comorbidities, or other psychiatric conditions. • 3 months treatment (selection based on clinical judgment.)	• A significantly lower level of CAT, NO, and GPX at baseline. • A significantly higher level of baseline MDA but No significant difference in the SOD level. • A significant improvement of NO and GPX levels after the treatment period.
Andreazza et al.,2007(22)	84/32	Blood	TBARs, SOD, CAT, GPX	Euthymia, mania, or depression.	• Exclusion criteria: other comorbidities, taking medications besides those prescribed for BD. • Patients were not smokers.	• A significantly higher level of TBARS, regardless of mood status. • A significantly higher SOD and SOD/(GPX+-CAT) ratio in manic and depressive patients. • A significantly lower level of CAT in manic or euthymic patients. • A significantly higher level of GPX only in euthymic patients.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Gergerlioglu et al.,2007(23)	29/30	Blood (baseline and after treatment)	NO, SOD	Mania	• Exclusion criteria: rapid cycler BD, taking antioxidants, substance abuse, head trauma, chronic somatic diseases, or seizures. • Receiving antimanic drugs or ECT as needed.	• A significantly higher level of NO (baseline and post-tr) • The SOD level (baseline and post-tr) was significantly lower. • Baseline SOD was significantly higher than Post-tr SOD in BD patients. • A significant negative correlation between baseline NO level and patient's sleep score. • A significantly higher level of NO (at baseline) can significantly increase delusionality incidence during mania. • A significant negative correlation between SOD level (post-tr) and the number of previous manic episodes.
Machado-Vieira et al.,2007(24)	45/30	Blood (baseline and follow-up)	TBARs, SOD, CAT	Mania	• Exclusion criteria: addiction, psychosomatic comorbidities, rapid cycler BD, experiencing a mixed episode, taking antioxidants. • 30 BD patients didn't receive medications. • 15 BD patients went under lithium treatment.	• TBARS and SOD levels were significantly higher in medication-free BD patients. • CAT level was significantly higher in all BD patients, especially in the lithium-treated group. • Lithium treatment can reduce SOD and increase CAT level, hence improves SOD/ CAT ratio.
Selek et al.,2008(25)	30/30	Blood (baseline and after treatment)	NO, SOD	Depression	• Exclusion criteria: substance abuse, head trauma, chronic somatic diseases, or seizures. • Receiving standard medications or ECT (as needed) to control the mood episode.	• A significantly higher level of NO at baseline, which improved after the treatment period. • The post-tr NO level was comparable to controls. • A significantly lower level of baseline SOD, which significantly increased after treatment. • Despite a noticeable improvement, post-tr SOD was significantly lower than controls.
Kunz et al.,2008(26)	83/32	Blood	SOD, TBARs	Euthymia, mania, or depression.	• Taking standard medications for BD.	• A significantly higher level of SOD in depressive and manic patients. • A significantly higher level of TBARS in all BD patients, especially manic BD.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Yumru et al.,2009(27)	94/41	Blood	TAC, TOC, OSI	Euthymia	• Exclusion criteria: Substance dependency, psychosomatic comorbidities, taking antioxidants.	• A significantly higher TAC, TOC, and OSI. • A significant negative correlation of TAC with the number of previous mood episodes.
Andreazza et al.,2009(28)	60/60	Blood	GST, GR	Not defined	• No noticeable comorbidities. • Only receiving medications to control BD (selection based on clinical judgment) • Based on disease duration (early and late stage), BD patients were divided into two groups.	• A significantly higher level of GST and GR in late-stage BD patients. • Direct association of GST and GR with the duration of disease.
Aksoy et al.,2010(29)	60/30	Blood	Myelo-peroxidase,MDA	Not defined	• 50% of BD patients also had ADHD. • Exclusion criteria: History of chronic somatic illnesses and serious head trauma.	• A significantly higher level of myeloperoxidase in patients with BD+ADHD but no statistical difference between BD patients (no ADHD) and controls. • A significantly higher malondialdehyde in BD patients ± ADHD.
Kapczinski et al.,2011(30)	60/80 *Positive control: 15 septic patients.	Blood	TBARs, PCC	Euthymia, mania, or depression.	• Exclusion criteria: severe illness, mental retards.	• Lipid and protein oxidation were significantly higher in manic and depressive BD patients. • Protein oxidation in BD patients was comparable to positive controls.
Raffa et al.,2012(31)	30/40	Blood	GSH, CAT, GPX	Not defined	• Exclusion criteria: dependence (except tobacco), taking vitamins, history of seizure or severe head trauma. • 22 patients under mood stabilizer drugs. Others were medication-free.	• A significantly lower level of serum GSH (total and reduced) and CAT. • No significant difference in serum GPX level.
Magalhaes et al.,2012(32)	55/94	Blood	TBARs, MDA, PCC	Not defined	• Patients with comorbidity or dependency were not excluded. • 76% of BD patients were experiencing depression, and 20% had mania.	• A significantly higher degree of protein oxidation in BD patients (especially in the manic state) • No significant difference in TBARS.
Lagopoulos et al.,2013(33)	53/51	Brain * H-MRS method	GSH	Not defined	• Exclusion criteria: nourological or somatic problems, cognitive or intellectual-related conditions, recent ECT. • 13% of BD patients were not taking any psychological drugs. Others were taking standard BD treatments ± anti-depressants.	• No significant difference in GSH level

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Soeiro-de-Souza et al.,2013(34)	50/50	Blood	8-OHdG	Mania or depression.	• Exclusion criteria: nourological or somatic problems, dependency, history of head trauma, and recent ECT. • Patients were free of any medications	• Oxidative damage to DNA guanosine bases was significantly greater. • Positive correlation of guanosine oxidation with the number of previous manic episodes.
Gubert et al.,2013(35)	12/30	Blood	TBARs, MDA, PCC	Euthymia	• Patients were under standard medications of BD.	• No significant difference in protein or lipid oxidation level
Godlewska et al.,2014(36)	13/11	Brain * MRS method	GSH	Euthymia	• Exclusion criteria: Other psychological or neurological conditions, using any medications besides OCPs, somatic comorbidities. • Patients were young and had no history of standard BD treatments.	• No significant difference in GSH level.
Versace et al.,2014(37)	24/19	Blood	Lipid hydrop-eroxide, 4-HNE	Euthymia	• Exclusion criteria: somatic or cognitive problems, history of head trauma, dependency, rapid cycler BD, IQ <85, borderline personality. • BD patients had a history of at least two mood episodes.	• A significantly higher level of lipid hydroperoxides but no difference in 4-HNE. • A negative correlation between lipid hydroperoxide level and white matter function in BD patients.
Aydemir et al.,2014(38)	51/50	Blood	MDA, NO, SOD, GSH	Euthymia	• Exclusion criteria: Substance abuse, neurological problems, psychosomatic comorbidities, taking antioxidants. • Only taking standard medications for BD.	• A significantly higher level of MDA and NO. • SOD level was significantly lower. • No significant difference in serum glutathione. • No significant relationship between oxidative stress and cognitive ability during remission.
de Sousa et al.,2014(39)	29/28	Blood (baseline and post-tr)	CAT, GPX, SOD, TBARs	Depression	• Exclusion criteria: psychosomatic comorbidities, history of head trauma, dependency, rapid cycler BD, recent ECT. Patients were medication-free at baseline and received lithium for six weeks.	• A significantly higher level of CAT and GPX. • No baseline difference in SOD and TBARS levels. • A significant reduction of SOD and TBARS after lithium therapy.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Cudney et al.,2014(15)	52/30	Blood	MDA, SOD, CAT, GST	Euthymia or depression	• Patients were all females.	• No significant difference in oxidative stress markers between controls and BD patients. • Within BD patients, circadian rhythms disturbance was significantly associated with higher lipid oxidation.
Rosa et al.,2014(40)	50/50	Blood	Oxidized glutathione and total GSH	Euthymia	• Patients with comorbidity or dependency were not excluded.	• A significantly lower level of total glutathione and a higher level of oxidized glutathione. • No significant difference in the BDNF level.
Bengesser et al.,2015(41)	113/78	Blood	MDA, TAC, PCC	Euthymia	• Exclusion criteria:chronic inflammatory diseases, neurodegenerative conditions.	• A significantly lower level of MDA and TAC in BD patients. • Carbonyl proteins were significantly high. • Within BD patients, the metabolic syndrome had no significant effect on oxidative markers though severe obesity was associated with a lower TAC level.
Tsai et al.,2015(17)	23/40	Blood (baseline and post-tr)	TBARs, GPX, SOD, CAT, 8-OHdG	Mania	• Exclusion criteria: heavy smokers, substance dependency, noticeable somatic diseases. • 20 cases received antipsychotics or mood stabilizers.	• A significantly higher level of TBARS. • A significantly lower GPX activity. • No significant difference in SOD, CAT, protein and DNA oxidation. • A Significant reduction of TBARS after pharmacotherapy.
Tunçel et al.,2015(42)	18/18	Blood	SOD, 8oxogua-nosine, 8-deox-yguano-sine, MDA, SOD, GSH, advanced oxidaton protein product	Mania or euthymia	• Exclusion criteria: drug abuse, smoking, and chronic comorbidities, BMI>25 kg/m2	• A significantly higher level of lipid peroxidation in manic patients. • Oxidized guanine species were significantly higher. • No significant difference in protein oxidation, serum SOD, and total glutathione
Hatch et al.,2015(43)	30/0 (non-controlled)	Blood	Lipid hydrop-eroxides, PCC	Not defined	• Exclusion criteria: recent infection, chronic diseases, inflammatory conditions, intellectual inability, psychosis. • Age between 13-19 years old • No current CVD.	• No significant correlation between oxidative stress markers and symptom severity. • Oxidative stress markers were significantly lower in BD patients of this study compared to adults with BD, based on previous literature.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Andreazza et al.,2015(44)	110/75	Blood	PCC, 3-nitrotyrosine, Lipid hydroperoxide, 4-HNE	Euthymia	• Exclusion criteria: neurological problems, dependency, dementia, recent ECT. • Age > 50 years old	• A significantly higher level of lipid hydroperoxide in BD patients. • No significant difference in protein oxidation
Chitty et al.,2015(45)	30/0 (Non controlled)	Brain * H-MRS method	GSH	Not defined	• Exclusion criteria: intellectual or cognitive disorders, somatic illnesses, neurological problems.	• Reduction in alcohol consumption was significantly associated with higher GSH. • No significant difference in GSH
Dubey et al.,2015(46)	32/30	Blood (baseline and post-tr)	MDA, SOD	Mania or mixed episode	• Exclusion criteria: addiction, other psychiatric or neurological conditions, serious somatic comorbidities, taking antioxidants. • Patients were medication-free at baseline and were treated with mood stabilizer drugs for six weeks.	• A significantly higher MDA at baseline. •The SOD and catalase activity was significantly lower (at baseline) • A significant reduction of MDA following mood stabilizer therapy.
Yirün et al.,2016(47)	51/43	Blood	TAS, TOS, OSI	Mania or euthymia	• Exclusion criteria: neurological or cognitive problems, psychosomatic comorbidities, dependency, TBI history, • Patients were not taking vitamins or antioxidants in the last six months.	• No significant difference in oxidative or antioxidative markers
Jacoby et al.,2016(48)	54/35	Urine (baseline and follow-up)	8-oxo-Guo, 8-oxo-deoxyguanosine	• Mania or mixed episode at baseline • Different mood states during follow-up.	• Exclusion criteria: noticeable medical problems, substance misuse, pregnant patients. • 6-12 months of follow-up.	• A significantly higher level of urinary 8-oxo-Guo in BD patients, regardless of mood state. • RNA and DNA oxidation were significantly higher in BD patients with mania/hypomania than euthymic subjects.
Mansur et al.,2016(49)	55/28	Blood	GPX, SOD	Euthymia or depression	• Exclusion criteria: Severe medical condition, substance misuse. • 54.5 % of BD patients had IGM	• A significantly higher activity of GSH-Px, which has a significant negative correlation with the number of mood episodes. • A significantly lower SOD level, which has a significant positive correlation with the number of mood episodes. • Among BD subjects, IGM significantly increases the GSH-Px level.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Mansur et al.,2016(50)	59/26	Blood	GSH-Px, SOD	Euthymia or depression	• Exclusion criteria: Severe medical condition, suicide intention, substance misuse, pregnancy, breastfeeding. • 49.15% of BD patients had IGM.	• Reverse association between BDNF and GSH-Px level. • Positive correlation between the level of BDNF and SOD. • IGM can significantly increase the GSH-Px level. • A significantly higher level of GSH-Px but no significant difference in SOD.
Siwek et al.,2016(51)	129/50	Blood	TBARs	Mania, hypomania, depression or euthymia.	• Exclusion criteria: substance abuse (besides nicotine and caffeine), other psychiatric conditions, chronic comorbidities, acute diseases, pregnant or breastfeeding women. • Taking standard medication to control BD.	• A significantly higher level of TBARS in BD patients during acute mood episodes (especially depression). • No significant difference in TBARS level between euthymic BD patients and controls.
Mondin et al.,2016(52)	48/94	Blood	TBARs	Not defined	• No specific exclusion criteria.	• No significant difference in the TBARS level between BD patients and controls. • BD patients with a late chronotype presented a significantly lower TBARS compared to other BD patients.
Akgün et al.,2017(53)	40/20	Blood	MDA, PCC	Not defined	• Exclusion criteria: substance abuse, other psychological or neurological conditions, somatic illnesses, immunological disorders • All BD patients were under valproate treatment, though 50% had MeS.	• A significantly higher level of protein carbonyls in all BD patients. • A significantly higher MDA level in BD+MeS subjects, compared to BD patients without MeS and controls. • A significantly lower level of thiols in BD patients without MeS, compared to BD+MeS and controls.
Nucifora et al.,2017(54)	62/48	Blood	GSH	Not defined	• Exclusion criteria: Chronic comorbidities, using supplements	• A significantly lower level of GSH.
Akarsu et al.,2018(55)	82/45	Blood	TOC, TAC, OSI	Mania	• Exclusion criteria: patients with previous depressive episodes, other psychological or somatic comorbidities. • Patients were medication-free at least one month prior to the inclusion.	• A significantly higher level of TOC, TAC, and OSI. • The TOC level in BD patients with the first manic episode was significantly higher than those with a history of several manias.

Table 1. Continued

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Erzin et al.,2018(56)	94/44	Blood	Thiol, disulfide	Mania or euthymia	• Exclusion criteria: Obese patients, pregnant women, intellectual inability, somatic illnesses, history of ECT.	• A significantly Lower level of thiols (total and naive), especially in a manic phase • No significant difference in serum disulfide level and disulfide/total thiol ratio.
Ngamchuea et al.,2018(57)	22/20	Saliva	GSH, Oxidized GSH	Euthymia	• No specific exclusion criteria. • 19 BD patients were under standard treatments to control BD.	• A significantly higher level of GSH and oxidized GSH but no significant change in their ratio. • No significant correlation between disease severity and glutathione level.
Valvassori et al.,2018(58)	51/0 Not controlled	Blood	SOD, TBARS, PCC, 3-nitroty-rosine	Euthymia or depression	• No specific exclusion criteria.	• A significantly higher level of superoxide species, SOD, protein, and lipid oxidation in depressive patients. • A significantly weaker performance of mitochondrial complex II in depressive patients.
Maes et al.,2019(59)	68/54	Blood	CAT, SOD, Lipid hydroperox-ide,MDA, advanced oxidaton protein product	Euthymia	• Exclusion criteria: Pregnancy, neurodegenerative disorders, other psychiatric conditions, immunocompromising, or chronic diseases. • Patients were not taking any of the following drugs: NSAIDs, GCs, interferon, herbal therapies, antioxidant or omega3 supplementation.	• Type 1 BD patients showed a significant elevation of protein oxidation. • A significant correlation between protein oxidation and BD type 1 severity. • A significantly lower level of SOD in type 2 BD patients. • A significantly higher lipid hydroperoxides in BD patients
Lv et al.,2019(60)	61/49	Blood	SOD, MDA, GSH-Px, CAT	Depression or mania	• Exclusion criteria: Severe somatic comorbidities, pregnancy (or intention of it), other psychiatric disorders, substance abuse, recent ECT therapy, taking antioxidants or vitamins. • Patients received lithium for six weeks.	• A significantly lower SOD activity and a higher MDA level in depressive BD. • A significantly higher level of GSH-Px activity in all BD patients. • No significant difference in the CAT level. • Lithium therapy significantly improved GPX and MDA levels.

First Author, Year	BD patients/ healthy controls (numbers)	Sample type	Assessed marker	Mood episode	BD Patients characteristics	Results *Compared to controls*
Knorr et al.,2019(61)	86/44	CSF and urine	8-oxo-Guo 8-oxo-de-oxyguano-sine	Euthymia at baseline	• Exclusion criteria: Severe somatic illnesses, pregnancy (or intention of it), substance abuse.	• RNA oxidative-damage was significantly higher in CSF and urine samples of BD patients at baseline and after a one-year followup. • A new mood episode during followup can significantly increase RNA damage. • No significant difference in DNA damage.
Demir et al.,2019(62)	42/55	Blood	NO, OSI	Mania	• Exclusion criteria: drug/ alcohol abuse, somatic illnesses, pregnancy, intellectual disability, TBI history, taking antioxidants or inhibitors of xanthine oxidase.	• A significantly higher level of urotensin II, nitric oxide, and oxidative stress index. • A positive but weak association between urotensin II and oxidative stress index.
Lv et al.,2020(63)	28/49	Blood (baseline and post-tr)	MDA, GPX, SOD	Mania or depression	• Exclusion criteria: Severe somatic comorbidities, pregnancy (or intention of it), other psychiatric disorders, substance abuse, recent ECT therapy, taking antioxidants or vitamins. • BD patients were diagnosed as treatment-resistant and went under six weeks of ECT treatment.	• A significantly lower level of baseline SOD. • A significantly higher level of baseline MDA and GPX. • No significant difference in baseline catalase level. • ECT therapy significantly decreased MDA, only in the responders.

Abbreviations: SOD: Superoxide dismutase/MDA: Malondialdehyde/NO: Nitric oxide/CAT: Catalase/GSH: Glutathione/GPX: Glutathione Peroxidase/TBARS: Thiobarbituric acid reactive substances/Post-tr: Post treatment/ECT: Electroconvulsive therapy/GR: Glutathione reductase/GST: Glutathione S-transferase/ADHD: Attention deficit hyperactivity disorder/4-HNE: 4-Hydroxynonenal/OCP: Oral contraceptive pill/PCC: Protein carbonyl content/8-oxo-Guo: 8-oxo-guanosine/MeS: Metabolic syndrome/CSF: Cerebrospinal fluid/NSAID: Nonsteroidal anti-inflammatory drug/GC: Glucocorticoid/IGM: impaired glucose metabolism/TAC: total antioxidant capacity/TOC: total oxidant capacity/OSI: oxidative stress index/H-MRS: Proton magnetic resonance spectroscopy/MRS: Magnetic resonance spectroscopy

Discussion

Bipolar disorder is a persistent mental disorder that interferes with patients' personal and social life. There are various hypotheses regarding the pathophysiology of Bipolar disorder, including oxidative stress (1). Oxidative stress can damage neural structure and function, particularly in the brain that contains a noticeable amount of oxidation-prone elements like myelin and iron (64).

Several post-mortem studies confirmed oxidative-related brain damage in BD patients. Gawryluk et al., compared post-mortem specimens of psychiatric patients' prefrontal cortex (including bipolar disorder) with healthy controls and demonstrated that the brain's Glutathione level was significantly lower in BD patients (65). Andreazza et al., analyzed post-mortem samples of the prefrontal cortex to examine the amount of oxidative damage. Oxidative damage to myelin and synaptosomal proteins was significantly higher in BD patients compared to healthy controls. Hence we can presume that oxidative stress can endanger normal signal transduction between neurons (9). In addition, in 2008, Andreazza et al., did a meta-analysis on clinical studies, most frequently observational types, and reported that the level of TBARs and NO were significantly higher in bipolar patients, which supports the oxidative stress in bipolar disorder. However, antioxidant enzymes were not significantly different between bipolar patients and healthy subjects (14) Since this article was published in 2008, several studies were published afterward, which may change the results. Hence, we did this review to get a better understanding.

In Table 1, we summarized clinical studies investigating

oxidative/antioxidative markers in BD patients. A majority of the studies that worked on oxidative markers (listed above) showed a significant elevation. On the other hand, studies that evaluated antioxidative markers showed more variations, especially in SOD and GSH-Px levels. To specify, twenty-six studies evaluated lipid peroxidation with lipid hydroperoxide, TBARs, and MDA markers. Seventy-three percent of them showed that lipid peroxidation is significantly higher in bipolar patients compared to healthy subjects.

Eleven studies evaluated protein oxidation using Protein carbonylation content or advanced oxidation protein products. Seven of them showed that bipolar disorder is associated with higher protein oxidation and three studies showed no significant difference. One of the studies had no control group, which does not allow us to compare bipolar patients with healthy controls (43). However, this study compared adolescent bipolar patients with adult ones and displayed that oxidative stress is lower in adolescent patients.

Four out of five studies that assessed nucleic acid oxidation (using 8-oxo-guanosine or 8-oxo-deoxyguanosine) reported an elevation of DNA/RNA oxidation in bipolar patients, compared to healthy controls. This supports the theory of neuronal dysfunction and apoptosis due to gene alterations. However, one study showed no significant difference in nucleic acid oxidation (17). Nevertheless, this study had only 23 bipolar patients, which affects the results. In addition, five out of six articles that measured nitric oxide reported an elevation of NO in bipolar patients, which supports the increase of oxidative stress. Overall, considering that the majority of studies showed that oxidative markers are higher in bipolar subjects compared to the control group, we can assume that oxidative stress theory is supported. However, more high-quality cohorts and meta- analyses are required to verify this assumption.

Twenty studies measured superoxide dismutase, but the results were remarkably incompatible. While five studies showed an elevation in SOD level, eight studies expressed a reduction of SOD in bipolar subjects. Seven studies displayed no significant difference between the patients and control groups. The same conflict applies to catalase marker. Out of eleven articles that measured catalase level, two studies reported an elevation, and five studies showed a reduction of catalase in bipolar subjects. The rest of them expressed no difference compared to healthy controls. We ought to consider that SOD and CAT act inter-dependently. SOD reduces free radicals to H2O2 and O2. Since H2O2 is still a toxic substance, it must be converted to water by the catalase enzyme (64). Therefore, SOD/catalase balance is essential for maintaining body homeostasis. If one of these two factors changes, the balance collapses, and oxidative stress happens.

Twenty-one studies evaluated glutathione and glutathione-related enzymes, such as glutathione peroxidase and glutathione reductase. The results of these studies were remarkably conflicting. Eight articles reported an elevation, and eight studies showed no significant difference in GSH-related enzymes between bipolar cases and control subjects. On the other hand, five studies showed that glutathione level was significantly lower in bipolar patients. There can be two explanations for these results. The first one is that the reduction of glutathione decreases the ability of the human body to compensate free radicals, which induce oxidative stress. On the contrary, glutathione levels may increase as a compensating response to the elevation of ROS and tries to naturalize this imbalance. According to these assumptions, we can explain this variance. Nevertheless, more accurate studies are required to support these theories because the studies that we included are very heterogeneous with a low-medium quality.

Seven studies used pharmacotherapy as an intervention to evaluate its effect on oxidative stress markers (17,21,23-25,39,46). These studies were not randomized and used the pre-post method. This design increases the risk of bias. However, these studies can be an implication for further investigations. According to our review, pharmacotherapy was beneficial in reducing oxidative stress, particularly lipid peroxidation, in bipolar patients. Although, these studies were very different in design, sample size, treatment period and type of medications, and etc. As a result, we can only consider these studies as a hypothesis and use them to design more homogenous studies with a defined intervention and higher quality.

The presence of confounding variables is another essential factor to be considered in the evaluation of clinical studies. As a result, we should consider the fact that oxidative homeostasis can be affected by many variables. This affects the outcome of studies and increases the risk of bias. For instance, inflammation and oxidative stress are highly correlated. Inflammatory processes increase ROS production, while oxidative stress can trigger pro-inflammatory mediators. Hence, BD patients with comorbid inflammatory conditions like infections or chronic diseases may present higher oxidative imbalance (6). Based on several studies, neurodegenerative disorders and psychiatric conditions like schizophrenia are associated with an oxidative imbalance (8, 66). Overall, to gain more specific data, patients with listed comorbidities should be excluded from clinical studies.

Another critical factor is the patient's drug history. As mentioned earlier, the use of medications to control mood episodes in bipolar patients can lower oxidative stress. According to this, patients who receive therapy are not actually comparable with drug-naive ones. In addition, it seems that euthymic patients present a more balanced oxidative status compared to manic or depressive patients. Therefore, detailed drug history and mood evaluation are required to get better results in clinical studies. Also,

subjects should have a matching lifestyle. Based on several studies, lifestyle-related factors such as obesity, changes in circadian rhythms, substance abuse, impaired glucose metabolism, and etc., can alter the oxidative status and should be considered in future study designs (16, 49, 52, 67).

One of the limitations of this review is that we considered all the studies that assessed oxidative markers in bipolar patients, regardless of potential confounding factors. This increases the risk of bias and impacts our outcomes. Besides, most of the included articles were cross-sectional, which has a low quality and does not specifically demonstrate the cause/outcome relationship. Nevertheless, this study considered many oxidative markers and antioxidant enzymes, which widens the scope of research. In addition, we listed many different attributes of the articles, such as sample type and inclusion/exclusion criteria, to achieve a more accurate conclusion. Overall, we recommend further high-quality cohorts with defined inclusion/exclusion criteria to minimize the impact of confounding variables and achieve a better understanding of the relationship between oxidative stress and bipolar disorder.

Conclusion

A majority of studies show an imbalance in oxidative status. Since several variables can alter these studies' results, we recommend further controlled-clinical studies with a large sample volume and precise exclusion criteria, including psychological/somatic comorbidities, substance abuse, etc. To get optimum results, patients should be comparable in lifestyle characteristics, mood status, and drug history.

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