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Review

Oxidative stress markers in affective disorders

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Abstract:
Affective disorders are a medical condition with a complex biological pattern of etiology, involving genetic and epigenetic factors, along with different environmental stressors. Increasing numbers of studies indicate that induction of oxidative and nitrosative stress (O&NS) pathways, which is accompanied by immune-inflammatory response, might play an important role in the pathogenic mechanisms underlying many major psychiatric disorders, including depression and bipolar disorder.
Reactive oxygen and nitrogen species have been shown to impair the brain function by modulating activity of principal neurotransmitter (e.g., glutamatergic) systems involved in the neurobiology of depression. Both preclinical and clinical studies revealed that depression is associated with altered levels of oxidative stress markers and typically reduced concentrations of several endogenous antioxidant compounds, such as glutathione, vitamin E, zinc and coenzyme Q10, or enzymes, including glutathione peroxidase, and with an impairment of the total antioxidant status. These oxidative stress parameters can be normalized by successful antidepressant therapy. On the other hand, some antioxidants (zinc, N-acetylcysteine, omega-3 free fatty acids) may exhibit antidepressant properties or enhance standard antidepressant therapy. These observations introduce new potential targets for the development of therapeutic interventions based on antioxidant compounds. The present paper reviews selected animal and human studies providing evidence that oxidative stress is implicated in the pathophysiology and treatment of depression and bipolar disorder.

Key words:
oxidative stress, marker, depression, affective disorders, bipolar disorder

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Introduction

Oxidative stress is defined as a persistent imbalance between antioxidants and pro-oxidants processes in favor of the latter. The result of this phenomenon is the excessive production of free radicals, the reactive oxygen species (ROS) [82]. At low, physiological concentrations ROS may function as signaling molecules, play important role in the immunological response and participate in the regulation of various cell activities (e.g., mitosis). However, in high concentrations reactive oxygen species lead to damage of components of the cell, including proteins (enzymes, receptors), lipids and DNA, which consequently may lead to apoptosis and cell death [31–33, 54].

Recent studies have shown that oxidative stress in combination with the pro-inflammatory mechanism plays an important role in the development of certain aging-associated diseases (e.g., cancer, cardiovascular disease and neurodegenerative diseases – such as Parkinson's and Alzheimer's disease), as well as psychiatric disorders, including depression, bipolar disorder, and schizophrenia [31–33].

The relationship between oxidative stress and the development of affective disorders may arise from the fact that the nervous system is particularly vulnerable to oxidative damage, due to: the high utilization of oxygen resulting in the production of free radicals, a high content of lipids (including unsaturated fatty acids) as a substrate for oxidation, redox potential of a number of neurotransmitters, inefficient defense mechanisms against free radicals, besides a high concentration of metal ions (e.g., iron, copper) involved in redox reactions [31–33, 64, 77, 95].

Furthermore, oxidative stress can damage the central nervous system by induction of excitotoxicity mechanisms mediated by glutamate and hyperstimulation of NMDA receptors [31, 32].

Based on a number of clinical and preclinical data, Maes et al. [58] formulated a hypothesis that activation of inflammatory pathways together with oxidative and nitrosative stress may form the pathophysiological basis of depression. Apart from tissue damage and its consequences, O&NS may cause an autoimmune response.

Oxidative and nitrosative stress may alter the chemical structures of various molecules and consequently generate a variety of modified new epitopes, which are highly immunogenic. For example, nitration of proteins leads to the formation of nitrotyrosine, a strongly immunogenic neoepitope. In turn, oxidation fatty acid autoepitopes, which are normally hidden from the immune system, can result in recognition by immune cells, once the lipid membrane components are damaged by oxidative processes. This explain why O&NS may generate an immunoglobulin (IgG or IgM)-mediated autoimmune response directed against the fatty acid and protein neoepitopes [55].

These phenomena, together with the oxidative and nitrosative damage to DNA, mitochondria and enzymes, can lead to neuronal dysfunction and their death or the development of neurodegenerative changes [53, 54, 57].

In the case of bipolar disorder, the relationship of its pathogenesis to oxidative and nitrosative stress (with the exception of the above-mentioned hypotheses) also indicates a broad mitochondrial dysfunction. These organelles are the place with the most intense oxidative processes and are the main source of free radicals [31–33].

Bipolar disorder is multi-dimensionally associated with mitochondrial dysfunction, as evidenced by: 1) comorbidity with mitochondrial diseases, 2) the occurrence in patients with bipolar disorder of mitochondrial DNA mutations and specific polymorphisms of mitochondrial genes, 3) the effect of mood stabilizers on mitochondrial metabolism [8, 10, 42, 81].

In accordance with Kapczinsky et al. [39], altered activity of markers and the accumulation of the negative effects of oxidative stress, together with the change of the neurotrophins' concentration and activity of certain immune and inflammatory markers, and alongside progressive neurostructural changes, reflects the successive stages of the biological and clinical advancement of bipolar disorder. The above-mentioned phenomena are interrelated and form the basis of the concept of affective disorders as a result of allostasis [20, 39, 40, 60].

Clinical trials are the source of indirect evidence of the participation of oxidative stress in the pathogenesis of affective disorders, and they also show the additional antioxidant effects of antidepressants or mood stabilizers. In many studies (but not all), the normalization of oxidative stress parameters after successful pharmacotherapy of affective episodes was observed [7, 64] (for details see Tabs. 2 and 3). On the other hand, some antioxidants also exhibit antidepressant properties.

N-acetylcysteine (NAC), a precursor of glutathione and glutathione pathway upregulator [18], in a dou-

ble-blind randomized placebo-controlled clinical study of the treatment of bipolar depression, significantly improved the efficacy of standard therapy [9], which was also indicated in systematic review [74].

Zinc (a trace element, whose relationship with oxidative stress, inflammatory mechanisms of depression, and the regulation of glutamatergic transmission is particularly well studied) has demonstrated both antidepressant activity and the ability to enhance the effect of antidepressants in animal studies [91, 92]. Similar potentiating effects of zinc were also observed in clinical trials, especially in the case of drug-resistant depression [65, 83]. Both animal studies and clinical observations have shown an association between changes in the concentration of blood zinc and the occurrence of depressive symptoms [84, 86, 91].

Omega-3 free fatty acids (FFA), known for their antioxidant properties, may be useful in monotherapy or adjunct treatment of unipolar or bipolar disorders [97]. Recent meta-analyses have shown that FFA are effective against major depression (supplements containing EPA ≥ 60% of total EPA + DHA combination) and bipolar depression [75, 90].

Moreover, potentiation of standard antidepressant treatment using the FFA may also be beneficial in drug-resistant unipolar or bipolar disorders [46].

Other antioxidants, such as Ebselen (the substance that mimics the activity of glutathione peroxidase) and liquiritin (a substance derived from *Glycyrrhiza uralensis)*, have also antidepressant effects observed in animal studies [63, 69, 104].

Measurement of oxidative stress

The main reactive oxygen species include: superoxide radical ($^{\bullet}O_2^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($^{\bullet}OH$). It should be noted that reaction between ROS and NO may result in nitrogen species production (e.g., peroxynitrite, $ONOO^-$), which are also potentially dangerous for the cell structures and enzymes [7, 34].

The main source of ROS in the human body are the processes of oxidative phosphorylation in the mitochondria and, to a lesser extent, the activity of enzymes such as xanthine oxidase (XO), NADPH oxidases, and cytochromes P450 (CYPs). Because reactive oxygen species have extremely short half-lives they are difficult to measure directly. Therefore, it is necessary to search for and determine the indirect markers of oxidative stress. An indicator of the intensity of oxidative stress might be the level or activity of the main enzymatic and nonenzymatic oxidant scavengers, the level of lipid, protein and DNA peroxidation/damage markers. Also, the activity of enzymes generating or related with ROS generation can be measured. Moreover, a good indicator of oxidative and nitrosative stress in the body are measurements of IgG-mediated responses to oxidized LDL or IgM-responses to products of nitration reactions, such as: nitrotyrosine (NO-tyrosine), NO-tryptophan and NO-arginine [55]. Additionally, various methods of total antioxidant potentials estimations can be used [7, 31–34, 100] (see Tab. 1).

Oxidative stress markers – animal (preclinical) studies

Stress-associated, experimental models of depression (parallel to clinical observations in humans) are accompanied by a decrease in antioxidant levels (enzymatic or non-enzymatic) and increased oxidative damage to fatty acids and proteins. In the olfactory bulbectomy model of depression in rats, the blood catalase (CAT) and glutathione (GSH) peroxidase (GSH-PX) activities were significantly decreased, while the superoxide dismutase (SOD) activity was increased. Chronic desipramine treatment significantly increased the activity of GSH-PX, without effect on the activity of SOD. Conversely, lithium treatment leads to SOD activity normalization, without impact on GSH-PX activity [87]. In turn, chronic unpredictable mild stress (CUMS) in mice resulted in elevated liver malondialdehyde (MDA), reduced total antioxidant capability (TAC), GSH level, SOD and CAT activities [103]. In chronic mild stress (CMS)-induced depression in the rodent, lowered concentrations of brain GSH were observed [68]. In another study, CMS resulted in a significant decrease in GSH-Px activity, and reduced GSH and vitamin C in the male Wistar rat's cortex, which was increased by lamotrigine, aripiprazole and escitalopram administration [19]. Moreover, the elevated plasma and brain lipid peroxidation levels were decreased after the administration of the three drugs mentioned above [19].

Tab. 1. Oxidative stress markers

Enzymatic antioxidant defences	Superoxide dismutase Catalase Glutathione peroxidase Glutathione reductase
Nonenzymatic antioxidant defences	Glutathione Vitamin A Vitamin C Vitamin E Coenzyme Q10 Zinc Albumin
Markers of lipid peroxidation and damage	Malondialdehyde Thiobarbituric and reactive substances 4-Hydroxynonenal F2- Isoprostanes
Markers of protein peroxidation and damage	Level of carbonyl groups, (protein carbonyl content)
Markers of DNA, RNA damage	8-Hydroxydeoxyguanosine 8-Hydroxyguanosine
Enzymes generating or related with $O_2^{\cdot-}$ generation	Xanthine oxidase NADPH oxidases Adenosine deaminase
Total antioxidant potentials	Total antioxidant capacity Total-radical nonenzymatic antioxidant potential Oxidative stress index Total oxidant status
Others	Prolidase Nitrostative damage markers: • NO, NO-tyrosine • Asymmetric dimethylarginine

Study based on: [14, 16, 31–34, 37, 53, 78, 102]

In studies by Lucca et al. [50, 51] CMS in rats resulted in lower SOD activity in the prefrontal cortex, the hippocampus and the striatum, plus increased catalase activity in the cerebellum, hippocampus, striatum, and the cortex. Likewise, increased lipid peroxidation in the cerebellum and the striatum and protein oxidative damage in the prefrontal cortex, hippocampus and striatum were observed. De Souza et al. [15] observed a decreased plasma GSH level and increased levels of thiobarbituric acid reactive substances (TBARS) after swimming or restraint stress procedures in female rats.

In the animal model of mania, amphetamine exposure resulted in raised TBARS and protein oxidation markers' levels in the rat brain [23]. Chronic amphetamine administration also increased superoxide production in submitochondrial particles of the prefrontal cortex and hippocampus in rats [24]. Additionally, acute or chronic amphetamine administration lead to SOD and CAT activity changes in the prefrontal cortex, hippocampus and striatum [25].

Oxidative stress markers – human (clinical) studies

A detailed summary of studies on the oxidative stress markers in unipolar and bipolar disorder are presented in Tables 2 and 3, respectively.

Major Depressive Disorder (unipolar)

An increasing number of reports indicate that frequently observed phenomenon in the depressive episode is oxidative damage to lipids [11, 17, 26, 41, 45, 73, 80, 85, 89, 98].

The first study (suggesting an association of depression with lipid peroxidation) showing lowered polyunsaturated fatty acid (PUFAs) in red blood cells membranes of depressed patients indicating an increased long-chain degradation *via* peroxidation [55]. Maes et al. computed the oxidative potential index (OPI) as an index to estimate the tendency of fatty acids to oxizide. There is evidence that depression is accompanied by significantly lowered OPI, suggesting that the potential of phospholipids to be oxizided is decreased. This could be the consequence of previously increased long-chain degradation *via* peroxidation [55].

In a study by Stefanescu and Ciobcia [89], the concentration of MDA (a byproduct of polyunsaturated fatty acids peroxidation and arachidonic acid) was more elevated in patients with recurrent depression than those with the first episode of depression. In some studies, lipid peroxidation markers were decreased after the successful antidepressant therapy, particularly in long-lasting (12–24 weeks) observations [11, 41, 45]. In an acute depressive episode, oxidative DNA damage markers in blood and urine as well as in the brain tissue of patients have also been detected [12, 21, 56]. Furthermore, in post mortem

Tab. 2. Summary of studies on the oxidative stress markers in patients with Major Depressive Disorder

Authors (year)	Patients	Findings	Sample
Sarandol et al. 2007 [73]	MDD = 96 HC = 54	Acute depressive phase: ↑ $MDA^{pl, rbc}$, SOD^{rbc} , Vit E^{pl} ↓ TAC^{pl} (+) correlation: MDs&SOD After 6 weeks of ADt*: No change	Blood – plasma, rbc
Cumurcu et al. 2009 [13]	MDD = 57 HC = 40	Acute depressive phase: ↑ TOS, OSI ↓ TAC After 12 weeks of Adt*: ↓ TOS, OSI ↑ TAC (+) correlation: MDs&TOS, OSI (–) correlation: MDs&TAC	Blood – serum
Gałecki et al. 2009 [26]	MDD = 50 HC = 30	Acute depressive phase: ↓ TAC^{pl} ↑ SOD^{rbc}, CAT^{rbc}, MDA^{rbc} ⟷ GPx^{rbc} After 12 weeks of Adt*: No changes	Blood – plasma, rbc
Gawryluk et al. 2011 [27, 28]	*Post mortem* MDD = 13 BD = 14 SCH = 14 HC = 12	↓ redGSH, oxGSH, total GSH in MDD, BD, SCH ↓ GPx in MDD and SCH ⟷ GST Pi in all ↓ GST Mu in MDD and SCH	Brain tissue – *prefrontal cortex*
Maes et al. 2009 [54]	MDD = 35 HC = 22	↓ CoQ10 (levels: HC MDD TRD) No correlation: MDs&CoQ10	Blood – plasma
Herken et al. 2007 [35]	MDD = 36 HC = 20	Acute depressive phase: ↑ ADA, XO ↓ SOD ⟷ NO No correlation: MDs & markers After 8 weeks of ADt*: ↑ SOD ↓ XO, NO	Blood – serum
Michel et al. 2010 [61]	*Post mortem* MDD = 7 HC = 7	↑ XO activity in the *thalamus* and *putamen*	Brain tissue – *hippocampus, regio entorhinalis, thalamus, putamen, caudate nucleus*
Dimopoulos et al. 2008 [17]	MDD = 33 HC = 33 (Subjects 60 year of age)	↑ 8-iso-PGF2a, IL-6	Blood – plasma
Maes et al. 2009 [55]	ME/SCF = 44 MDD = 25 ME/CSF+MDD = 23 HC = 17	↑ 8-OhdG in MDD + ME/CSF *vs.* others	Urine
Kaddurah-Daouk et al. 2012 [38]	dMDD = 14 rMDD = 14 HC = 18	In rMDD *vs.* others ↑ MET ↓ GSH/MET dMDD = HC	CSF
Khanzode et al. 2003 [41]	MDD = 62 HC = 40	Acute depression ↑ MDA^{ser}, SOD^{ser} ↓ Vit C^{pl} After 4 and 12 weeks of Adt* ↓ MDA^{ser}, SOD^{ser} ↑ $VitC^{pl}$	Blood – plasma, serum

Tab. 2. – *continued from the previous page*

Authors (year)	Patients	Findings	Sample
Bilici et al. 2001 [11]	MDD = 30 HC = 32	Acute depressive phase: ↑ $MDA^{pl, rbc}$, SOD^{rbc}, GPx^{rbc}, GR^{pl} After 12 weeks of Adt*: ↓ $MDA^{pl, rbc}$, SOD^{rbc}, GPx^{pl}, GR^{pl}	Blood – plasma, rbc
Kotan et al. 2011 [45]	MDD = 50 HC = 44	Acute depressive phase: ↑ MDA^{pl}, SOD^{rbc} ↓ ARL, ⟷ GPX^{ser}, Vit^{pl} A,C,E After 24 weeks of Adt*: ↓ SOD^{rbc}, TAC^{ser}, MDA^{pl} ↑ Vit A^{pl}	Blood – plasma, serum, rbc
Che et al. 2010 [12]	*Post mortem* MDD = 15 SCH = 15 BD = 15 HC = 15	In CA1, CA3 and dentate gyrus: ↑ 8-OhG (level: SCH BD MDD HC)	Brain tissue – *hippocampus*
Forlenza and Miller 2006 [21]	MDD = 84 HC = 85	↑ 8-OhdG recD sD HC	Blood – serum
Kobrosly and van Wijngaarden 2010 [43]	No D/ Mild D = 3080 Moderate D = 705 Severe D = 82	GGT – positively related to Mds Vit C – inversely related to MDs	Blood – serum
Kodydkova et al. 2009 [44]	Only woman MDD = 35 HC = 35	↓ GPx^{rbc}, GSH^{ser} ↑ SOD^{rbc}, Gr^{rbc} ⟷ CAT^{rbc}	Blood – rbc, serum
Gibson et al. 2012 [30]	MDD = 16 HC = 16	↑ PC, GR ⟷ GSH	human dermal fibroblast cultures
Irie et al. 2005 [36]	MDD = 30 HC = 60	↑ 8-OhdG (+) correlation: Mds & 8-OhdG	Blood – peripherial leukocytes
Maes et al. 2000 [58]	MDD = 42 HC = 26	↓ Vit E	Blood – serum
Owen et al. 2005 [66]	MDD = 49	↓ Vit E (–) correlation: MDs & Vit E	Blood – plasma
Tsuboi et al. 2006 [94]	Nurses HJS = 18 LJS = 15	↓ Vit E in HJS (+) correlation: Ds & MDA/LDL+VLDL	Blood – plasma
Stefanescu and Ciobica 2012 [89]	MDD = 31 • feMDD = 15 • recMDD = 16 HC = 20	↓ SOD, PGx (level: rMDD feMDD) ↑ MDA (level: rMDD feMDD)	Blood – serum
Michel et al. 2007 [62]	*Post mortem* MDD = 7 HC = 7	↑ SOD in prefrontal cortex ⟷ SOD in hippocampus	Brain tissue – *prefrontal cortex, hippocampus*
Szuster-Ciesielska et al. 2008 [93]	MDD = 29 HC = 30	↑ SOD^{ser}, CAT^{ser}, PER^{ser}, ROS^{pmn}	Blood – PMN, serum
Yager et al. 2010 [98]	MDD = 73 HC = 72	↑ 8-iso-PGF2a No correlation with MDs	Blood – serum
Rawdin et al. 2013 [72]	MDD = 20 HC = 20	⟷ 8-iso-PGF2a (+) correlation with IL-6 (–) correlation with IL-10	Blood – plasma

Tab. 2. – *continued from the previous page*

Authors (year)	Patients	Findings	Sample
Srivastava et al. 2002 [88]	MDD = 66 HC = 114	←→ SOD, CAT, GPx	Blood – PMN
Yanik et al. 2004 [99]	MDD = 21 HC = 28	↓ TAP, Vit C ↑ OSI, TP	Blood – plasma
Selley 2004 [80]	MDD = 25 HC = 25	↑ HNE, ADA	Blood – plasma

Abbreviations: (–) – inverse correlation; (+) – positive correlation; * – comparison to acute depressive phase; 8-iso-PGF2a – F2alpha-isoprostanes; 8-OhdG – 8-hydroxy-2'-deoxyguanosine; 8-OhG – 8-hydroxy-guanosine; ADA – adenosine deaminase; ADt – antidepressant treatment; ARL–- arylesteraze; BD – bipolar disorder; CAT – catalase; CSF – cerebro-spinal fluid; CoQ10 – coenzyme Q10; D – depression; dMDD – actually depressed; feMDD – first episode of depression; GPx – glutathione peroxidase; GR– glutathione reductase; GSH – glutathione (red – reduced, ox – oxidized); GST – glutathione S-transferase (Mu, Pi – isophorms); HC – healthy control, HJS – high job stress; HNE – (E)-4-Hydroxy-2-nonenal; IL-6 – intreleukin 6; IL-10 – interleukin 10; LBS – low job stress; LDL +VLDL – low density+ very low density lipoprotein; MDA – malondialdehyde; MDD – major depressive disorder (unipolar depression); MDs – major depression severity; ME/CFS – encephalomyelitis / chronic fatigue syndrome; MET – methionine; NO – nitric oxide; OSI – oxidative stress index; PC – protein carbonylation; PER – total peroxidase; pl – plasma, PMN – polymorphonuclear leukocyte; rbc – red blood cells; recD – recurrent depression; recMDD – reccurent MDD; rMDD – remitted MDD; ROS – reactive oxygen species; SCH – schizophrenia; sD – single depressive episode; SOD – superoxide dismutase; TAC – total antioxidant capacity; TAP – total antioxidant potential; TOS – total oxidant status; TP – total peroxide; TRD – treatment resistant depression; Vit A – vitamin A; Vit C – vitamin C; Vit E – vitamin E; XO – xanthine oxidase

studies, the 8-hydroxyguanosine (8-OhG) level was higher than of the control group, but lower than in patients with schizophrenia and bipolar disorder [12]. In other studies, Forlenza and Miller also showed elevated levels of 8-OhG in patients with recurrent depression when compared to patients experiencing their first episode of depression [21].

Another frequently reported phenomenon in depressed patients is a decreased concentration of antioxidants, such as vitamin E or coenzyme Q10 [41, 53, 55, 66, 99]. Despite this, there are a few reports in which (in acute episodes of depression) the levels of vitamins A, E and C remained unchanged when compared to healthy volunteers [45]. Besides, in one study, the vitamin E concentration was even higher [73]. In another research, a negative correlation between the blood concentration of vitamin E and the severity of depression was found [66], while another shows an inverse relationship between the severity of depression and vitamin C level [43]. According to some research, antidepressant drugs may increase the level of vitamin C or A when compared to a significantly reduced baseline value [41, 45].

The main systems that are synchronized with free radical processes and protect cells from damage caused by the free radicals are antioxidant enzymes, expressed both in the periphery and in the brain. Many studies indicate that the activity of these enzymes (including copper-zinc superoxide dismutase, catalase and glutathione peroxidase) in patients with unipolar disorder are usually different from those observed in healthy subjects. Most data show increased SOD activity in acute depression [11, 26, 41, 44, 45, 73, 94], while some others present opposite effects [35, 89]. In several studies, the normalization of superoxide dismutase activity after antidepressant treatment was observed [11, 35, 41, 45], besides a positive correlation between their activity and the severity of depression [73].

In the unipolar disorder, an increased activity of catalase and glutathione reductase (GR), and decreased activity of glutathione peroxidase (GPx), was demonstrated [11, 26, 30, 44, 93]. There are also reports in which there were no differences between patients and healthy controls [26, 44, 45, 88]. Antidepressant therapy resulted in the normalization of GR and GPx activity [11].

Other clinical studies show that in patients with a depressive episode the total antioxidant capacity is lower and the oxidative stress index or total oxidant status is higher than in healthy subjects [13, 26, 73, 99]. In one of the above studies, the total antioxidant potential was correlated with the severity of depression, and was normalized after the antidepressant treatment [13].

Tab. 3. Summary of studies on the oxidative stress markers in patients with bipolar disorder

Authors (year)	Patients	Findings	Sample
Savas et al. 2006 [76]	BD = 27 HC = 20	↑ NO, SOD (+) correlation: number of manic episodes & NO	Blood – serum
Andreazza et al. 2007 [2]	BD = 84 • M = 32 • D = 21 • Eu = 31	In M: ↑ S100B, SOD, TBARS, SOD/CAT + Gpx ⟷Gpx ↓ CAT In D: ↑ S100B, SOD, TBARS, SOD/CAT + Gpx ⟷GPx, CAT In Eu: ⟷S100B, SOD ↑ TBARS, Gpx; ↓ CAT	Blood – serum
Machado-Vieira et al. 2007 [52]	BD = 45 (M) • on lithium = 15 • unmedicated = 30 HC = 75	In unmedicated: ↑ TBARS, CAT, SOD ↓ NSE In lithium treated: ⟷TBARS, SOD, ↑ CAT ↓ NSE No correlation: markers & YMRS	Blood – plasma
Selek et al. 2008 [79]	BD-I = 30 (D) HC = 30	Acute phase: ↑ NO, ↓ SOD *After 30 days of treatment: ↓ NO, ↑ SOD	Blood – serum
Gergerlioglu et al. 2007 [29]	BD = 29 (M) HC = 30	Acute phase: ↑ NO, ↓ SOD *After 30 days of treatment: ⟷NO; ↓ SOD	Blood – serum
Abdalla et al. 1986 [1]	BD = 20 HC = 58	↑ SOD ⟷GPx	Blood – rbc
Kuloglu et al. 2002 [47]	BD = 23 HC = 20	↑ MDA^{pl}; SOD^{rbc} ⟷GPx^{rbc}	Blood – plasma, rbc
Ranjekar et al. 2003 [71]	BD = 10 HC = 27	⟷SOD^{rbc}, CAT^{rbc}, ⟷GPx^{rbc}, $TBARS^{pl}$	Blood – plasma, rbc
Frey et al. 2007 [22]	BD = 2 monozygotic tweens (M) HC = 1	Acute phase: ↑ TBARS, SOD, DNA dmg ↓ CAT *After 6 weeks of TR: ↓ TBARS, SOD, ⟷CAT, DNA dmg	Blood – serum
Ozcan et al. 2004 [67]	BD = 18 (M = 16; D = 2) HC = 21	↓ CAT, GPx, NO ↑ MDA	Blood – rbc
Magalhães et al. 2012 [59]	Early–stage mood disorders (PT – 18–24years of age) BD = 55 MDD = 82 HC = 94	In MDD: ⟷PCC, TBARS In BD: ↑ PCC ⟷TBARS Association of serum PCC level with current mania	Blood – serum

Tab. 3. *– continued from the previous page*

Authors (year)	Patients	Findings	Sample
Wang et al. 2009 [96]	*Post mortem* BD = 15 MDD = 15 SCH = 15 HC = 15	In BD, SCH: ↑ 4-HNE In MDD: ⟷ 4-HNE	Brain tissue – anterior cingulate cortex
Raffa et al. 2012 [70]	BD-I = 30 SCH = 46 HC = 40	In BD: ↓ GSH, redGSH, CAT ⟷SOD, GPx, oxGSH In SCH: ↓ GSH, redGSH, SOD (level: SCH BD), CAT (level: SCH BD), oxGSH ⟷GPx	Blood – plasma, rbc
Yumru et al. 2009 [101]	BD = 94 • BD-I = 45 • BD-II = 22 • AIM = 27 HC = 41	BD: ↓ TAS, TOS (BD-I BD-II), OSI In BD-I: ↑ TAS, TOS, OSI (–) correlation: TAS & number of episodes In BD-II: ↑ TAS ⟷TOS, OSI In AIM: ↑ TAS, TOS, OSI	Blood – plasma
Andreazza et al. 2007 [3]	BD-I (M, D) = 32 HC = 32	↑ DNA dmg	Whole blood
Selek et al. 2011 [78]	BD-I (M,D, Eu) = 66 HC = 66	↑ PRO (M = D = Eu)	Blood – serum
Banerjee et al. 2012 [6]	BD = 73 • LS = 48 • DN = 25 HC = 35	In BD: ↓ Na^+K^+ATPase ↑ TBARS	Blood – serum
Kunz et al. 2008 [48]	BD = 84 • D = 21 • M = 32 • Eu = 31 SCH= 97 H C= 32	In M: ↑ SOD, TBARS (level: M other groups) In D: ↑ SOD, TBARS In Eu: ⟷SOD ↑ TBARS In SCH: ↑ SOD, TBARS	Blood – serum
Lagopoulos et al. 2013 [49]	Young patients, early stage of illness (16–33 years of age) BD = 53 • BD-I = 13 • BD-II = 25 • BS = 15 HC = 51	⟷GSH No correlation: M or D severity or course of illness	*In vivo* –magnetic resonance spectroscopy (MRS) – anterior cingulate cortex

Tab. 3. – *continued from the previous page*

Authors (year)	Patients	Findings	Sample
Kapczinski et al. 2011 [39]	BD-I = 60 • Eu = 20 • D = 20 • M = 20 HC = 80 Septic patients = 15	↑ PCC, TBARS In D: ↑ PCC (level: D Eu, D M), TBARS (level: D Eu) In M: ↑ PCC(level: D Eu), TBARS (level: M Eu; M D) In Eu: ⟷PCC, TBARS	Blood – serum
Andreazza et al. 2010 [5]	*Post mortem* BD = 15 MDD = 15 SCH = 15 HC = 15	↑ PCC in BD ⟷PCC in MDD, SCH ↑ NT in BD, SCH	Brain tissue – prefrontal cortex
Siwek et al. 2013 [85]	BD = 34 • D = 24 • R = 10 MD = 41 • D = 31 • R = 10 HC = 22	↑ TBARS in D (MDD = BD) ⟷TBARS in R (MDD = BD)	Blood – serum

Abbreviations: * – comparison to acute phase; AIM- antidepressant induced mania; BD – bipolar disorder (I – type I, II – type II); CAT – catalase; D – depression; DN – drug naïve; DNA dmg – DNA damage; Eu – euthymia; GPx – glutathione peroxidase; GSH – glutathione (red – reduced, ox – oxidized); HC – healthy control; HNE – (E)-4-Hydroxy-2-nonenal; LS – Lithium stabilized; M – mania; MDA – malondialdehyde; MDD – major depressive disorder; NO – nitric oxide; NSE – neuron-specific enolase; NT – nitrotyrosine; OSI – oxidative stress index; PCC – protein carbonyl content; pl – plasma; PRO – prolidase; PT – patients; R – remission; rbc – red blood cells; S100B – calcium binding protein B; SCH – schizophrenia; SOD – superoxide dismutase; TAS – Total antioxidants status; TBARS – Thiobarbituric acid reactive substances; TOS – Total oxidant status

Bipolar disorder

A meta-analysis of 16 studies published up to September 2007, shows that the most commonly reported phenomenon in bipolar disorder (which is an indicator of oxidative stress) is elevated levels of thiobarbituric acid reactive substances (TBARS) and nitric oxide (NO) in the blood of patients, that were measured, depending on the study, and either treated or untreated with mania, depression or euthymia [4]. Also, our preliminary results demonstrate increased levels of TBARS in the acute phase of depressive symptoms both in patients with bipolar and unipolar disorder. While in patients in remission (both with bipolar and recurrent unipolar disorder), the TBARS concentration remained unchanged when compared to that measured in healthy volunteers [85]. Individual data also show no difference in the TBARS level between healthy volunteers and patients treated with lithium [52], or in patients with early-stage bipolar disorder or major depressive disorder [59]. Studies carried out on monozygotic twins showed the normalization of the TBARS levels after successful antimanic treatment [22]. The elevated levels of the lipids' peroxidation products, MDA and 4-hydroxynonenal (4-HNE), were determined in the blood serum of bipolar patients [47, 67, 96].

Similar to unipolar disorder, ROS-induced damage to DNA and proteins in bipolar disorder may also occur [3, 22]. One of these studies showed that the frequency and severity of DNA damage in samples isolated from patients was significantly higher than in the control group. Additionally, the severity of the damaging processes was positively correlated with the severity of the mania or depression [3]. An increase in the carbonylated protein content (PCC) is usually observed in bipolar disorder, including both the manic or depressive phases [5, 39, 59].

Data concerning activity of the free radical scavenger enzymes in bipolar disorder are relatively numerous, but generally contradictory. In various studies, it was observed in different phases of the disease that there was both a significant increase and decrease in the activity of these enzymes [1, 2, 4, 22, 29, 52, 67, 70, 71, 76, 79]. The most consistent and repeatable results concern the activity of superoxide dismutase (SOD). In most studies of bipolar disorder patients, the activity of this enzyme is increased when compared to healthy subjects [1, 2, 22, 47, 48, 52, 76]. However, it should be noted that these studies were usually conducted during a manic phase. In several studies on the effects of antidepressant therapy on antioxidant processes, a normalization of SOD activity was observed after the treatment with mood stabilizers [22, 79], or there were no changes in patients treated with lithium when compared to healthy controls [52].

Conclusions

The study of oxidative stress markers are a contribution to the search for a clinically useful markers of affective disorders. Currently, these studies mainly provide insight into the biological basis of depression and bipolar disorder, indicating a possible relationship of these disorders with neurodegenerative processes in different areas of the brain. However, further studies are needed to better understand the role of oxidative stress and antioxidants in the central nervous system and the potential therapeutic effects of antioxidants.

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