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Research paper

Evaluation of changes in carbonyl stress markers with treatment in male patients with bipolar disorder manic episode: A controlled study

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ABSTRACT

Background: Carbonyl stress, a metabolic state characterized by elevated production of reactive carbonyl compounds (RCCs), is closely related to oxidative stress and has been implicated in various diseases. This study aims to investigate carbonyl stress parameters in drug-free bipolar disorder (BD) patients compared to healthy controls, explore their relationship with clinical features, and assess the effect of treatment on these parameters.
Methods: Patients with a primary diagnosis of a manic episode of BD and healthy controls were recruited. Exclusion criteria included intellectual disability, presence of neurological diseases, chronic medical conditions such as diabetes mellitus and metabolic syndrome, and clinical signs of inflammation. Levels of serum carbonyl stress parameters were determined using high-performance liquid chromatography.
Results: Levels of glyoxal (GO) and methylglyoxal (MGO) did not differ between pre- and post-treatment patients, but malondialdehyde (MDA) levels decreased significantly post-treatment. Pre-treatment MGO and MDA levels were higher in patients compared to controls, and these differences persisted post-treatment. After adjusting for BMI and waist circumference, only MDA levels remained significantly higher in patients compared to controls.
Limitations: The study's limitations include the exclusion of female patients, which precluded any assessment of potential gender differences, and the lack of analysis of the effect of specific mood stabilizers or antipsychotic drugs.
Conclusions: This study is the first to focus on carbonyl stress markers in BD, specifically GO, MGO, and MDA. MDA levels remained significantly higher in patients, suggesting a potential role in BD pathophysiology. MGO levels were influenced by metabolic parameters, indicating a potential link to neurotoxicity in BD. Further research with larger cohorts is needed to better understand the role of RCCs in BD and their potential as therapeutic targets.

1. Introduction

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent mood shifts between depressive and manic episodes that affects approximately 1 % of the population. BD is associated with significant rates of recurrence, disability, and a substantial economic burden (McIntyre et al., 2020). Early diagnosis and treatment appear to be crucial in order to limit the negative outcomes of untreated illness. However, despite advancements in the field, the quest for objective markers that can inform on timely diagnosis, prognosis, treatment selection and treatment response remains unmet.

Oxidative stress has been consistently reported in patients with BD (Berk et al., 2011; Jorgensen et al., 2022), and elevated levels of reactive oxygen species (ROS) have been associated with the onset and

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progression of the illness (Jiménez-Fernández et al., 2021; Niedzielska et al., 2015). Increased oxidative stress has detrimental effects on signal transduction, synaptic plasticity, and cellular resilience, particularly by inducing lipid peroxidation in membranes, or oxidative damage of proteins and nucleic acids (Liu et al., 2017; Özerdem and Ceylan, 2022). Nucleic acid damage has been linked to the severity of depressive and manic symptoms in BD (Andreazza et al., 2007). A recent meta-analysis underscored the importance of increased lipid peroxidation in patients with BD (Almulla et al., 2023). Moreover, protein modification plays a crucial role in the pathogenesis of various diseases, including vascular complications, inflammatory conditions, as well as mental disorders (Jomova et al., 2023; Steckert et al., 2010). The association between increased oxidative stress in BD and exacerbated cognitive deficits further emphasizes its pivotal role in the pathophysiology of BD (Vieta et al., 2013). Current evidence also suggests that obesity or metabolic syndrome can complicate the symptoms and course of BD, highlighting a central role of oxidative stress in its pathophysiology (SayuriYamagata et al., 2017).

Carbonyl stress is closely related to oxidative stress and represents an abnormal metabolic state resulting from increased production of reactive carbonyl compounds (RCCs) such as glyoxal (GO), methylglyoxal (MGO), and malondialdehyde (MDA) (Twarda-clapa et al., 2022; Vistoli et al., 2013). RCCs are formed endogenously during lipid peroxidation and glycoxidation of carbohydrates, and can serve as precursors for the synthesis of advanced glycation end products (AGEs) and advanced lipid peroxidation end products (ALEs). These compounds form cross-links on tissular proteins, leading to carbonyl stress, and accumulate during aging and in chronic diseases (Moldogazieva et al., 2019). AGEs are generated as a consequence of elevated carbonyl stress and have been implicated in various diseases, including diabetes mellitus, chronic kidney disease, cardiovascular diseases, and cognitive impairment with or without dementia (Blake et al., 2023; Nin et al., 2011; Zeng et al., 2019). Oxidative stress induces lipid peroxidation and glycoxidation reactions, resulting in the formation of highly reactive and electrophilic compounds that can covalently modify free amino groups of proteins, generating ALEs and AGEs (Vistoli et al., 2013). Additionally, the induction of oxidative stress with RCCs can create a positive feedback loop that amplifies oxidative damage in the brain. The interaction of AGEs with their cell surface receptors such as receptor for AGE (RAGE) activates the AGE–RAGE axis, leading to the activation of NF-κB and the release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and interleukin-1 (Twarda-clapa et al., 2022). The accumulation of ALEs and AGEs ultimately induces severe cytotoxicity in neurons and can cause dysfunction of the nervous system. Recent studies in animals and humans have demonstrated that increased carbonyl stress was associated with neurotoxicity (Coccini et al., 2023), cognitive decline (Pucci et al., 2021), and schizophrenia (Juchnowicz et al., 2021; Ohnuma et al., 2018). However, to date, carbonyl stress has not been sufficiently examined in mood disorders.

The objectives of the current study were as follows: (i) to investigate the levels of carbonyl stress parameters (GO, MGO, and MDA) in drug-free patients diagnosed with manic episode of BD, and comparing them with healthy controls, (ii) to explore the relationship between the levels of carbonyl stress parameters and their relationship with clinical features in BD patients, and (iii) to assess the effects of treatment on carbonyl stress parameters in BD patients through pre- and post-treatment evaluations. We hypothesized that RCCs would be associated with the presence of a BD diagnosis, independent of cardiometabolic parameters. This would support a link between carbonyl stress and mood disorders. We also anticipated a significant decrease in carbonyl stress markers with treatment, which was evaluated by measuring the levels of these markers in both manic and euthymic phases.

2. Methods

2.1. Participants

This case-control study, which adopted a naturalistic follow-up design, was conducted between February 1, 2022, and March 1, 2023, at the inpatient psychiatric department of Basaksehir Cam and Sakura City Hospital in Istanbul, Turkiye. The diagnosis of the patient group was established upon consensus of two senior psychiatrists based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The inclusion criteria for patients were defined as follows: age between 18 and 60 years, and hospitalization with the primary diagnosis of a manic episode of BD. Patients were recruited if they met the inclusion criteria. The recruited patients were unmedicated, meaning that they had not taken any mood stabilizers or antipsychotics for at least four weeks prior to admission, which was required due to the index mood episode.

The healthy control group consisted of individuals attending the outpatient clinic for obligatory pre-employment psychiatric examinations, and underwent routine laboratory screening. Forty-one healthy volunteers, aged 18 to 60 years, were identified as control subjects. Based on the psychiatric interview and assessment of medical records, these healthy controls had no previous or current psychiatric diagnoses and no chronic medical illnesses. Additionally, it was ensured that the control subjects were not taking any prescribed or over-the-counter medications at the time of inclusion in the study or prior. The psychiatric interview investigated any family history of psychiatric illnesses, confirming that none of the control subjects had a first-degree relative with a psychiatric diagnosis. For both groups, the exclusion criteria were as follows: intellectual disability, neurological diseases and chronic medical conditions such as diabetes mellitus, metabolic syndrome and chronic hepatic or renal failure, as these conditions are known to be associated with increased formation of AGEs (Hanssen et al., 2019; Yozgatli et al., 2018). Hypertension, acute or chronic immuno-inflammatory diseases, and clinical signs of inflammation (CRP $\geq$ 5 μg/ml) and/or leukocytosis (>10,000 G/I) were also set as the exclusion criteria.

The current study recruited only male individuals in both patient and control groups to maintain homogeneity of the data and to rule out female-specific hormonal oscillations that may influence the levels of the markers. Although there is no specific data directly linking sex steroid hormones to carbonyl stress parameters, it is known that both estrogen and progesterone can influence oxidative stress homeostasis through various mechanisms (Chainy and Sahoo, 2020). For example, progesterone can reduce free radical formation and strengthen the endogenous free radical scavenging and antioxidant system. This can decrease lipid peroxidation, which is manifested by a decrease in the products of lipid peroxidation; the same markers that were evaluated in the current study (Zampieri et al., 2009). Additionally, estradiol has been shown to play an important role in balancing oxidative stress in various tissues by modulating the endogenous antioxidant defense system (Prokai-Tatrai et al., 2008). Modulation of oxidative stress can also affect carbonyl stress formation. Therefore, any alteration in oxidative stress may also closely affect the carbonyl stress markers that we have aimed to detect (Vistoli et al., 2013). For these reasons, female patients were not included in the current study.

Initially, 62 patients with BD who were hospitalized in our inpatient unit were enrolled to study. Seven patients were excluded due to the presence of psychiatric comorbidities, including substance use, and three patients were excluded due to the presence of active infectious diseases or a documented systemic illness. The criteria for metabolic syndrome were assessed in accordance with the National Cholesterol Education Program Adult Treatment Panel III guidelines (Lipsy, 2003). Following the clinical assessment, an additional four patients were newly diagnosed with metabolic syndrome and were subsequently excluded from the study. Finally, 48 patients and 41 healthy controls

matched with the study group for age were included.

2.2. Procedure

Written informed consent was obtained from all study participants, and the study protocol was approved by the local Ethics Committee (IRB: [14.03.2022–2022.03.75]). Data collection was carried out using a study-specific form derived from clinical charts, electronic medical records, and psychiatric interviews. The form included socio-demographic, historical, and clinical variables, as well as characteristics of bipolar disorder such as duration of illness, number of episodes, and previous hospitalizations. In addition to the RCCs as carbonyl stress markers, routine blood sampling for both the patient and control groups was carried out at admission, including measurements of fasting glucose, creatinine, and blood urea nitrogen (BUN). Renal function was assessed through glomerular filtration rates (normal >60 ml/min) and urinalysis. Additionally, serum lipids, waist circumference, blood pressure, and fasting glucose were measured at admission. All subjects were free of significant cardiovascular events, as determined by clinical history, cardiovascular examination, and electrocardiogram.

The severity of mania was evaluated using the Young Mania Rating Scale (YMRS), a widely employed tool for assessing the intensity of manic episodes. The scale comprises of 11 items derived from both the patient's subjective reporting and psychiatric examination (Young et al., 1978). YMRS assessments were conducted both at admission and at the time of discharge (for the patient group only). A euthymic state was defined as a YMRS score below 8, aligning with the criteria outlined by the International Society for Bipolar Disorders Task Force for symptomatic remission (Tohen et al., 2009).

2.3. Measurement of reactive carbonyl compounds

Blood samples were obtained from all participants by venipuncture after a 12-h overnight fast. Specimens from patients were taken pre-treatment as well as post-treatment when they reached a euthymic state. The tubes in which the blood samples were collected were centrifuged at 2000 Å ~ g, for 10 min at room temperature. The obtained serum was stored at −80 °C and thawed only once prior to analysis. The levels of serum carbonyl stress parameters were determined using high-performance liquid chromatography (HPLC). GO (40 %), MGO (40 %), tetraethoxypropane, trichloroacetic acid (TCA), thiobarbituric acid (TBA), 4-nitro-1,2- phenylenediamine, methanol, and acetonitrile were obtained from Sigma-Aldrich (St. Louis, MO, USA).

2.3.1. Analysis of glyoxal and methylglyoxal

For the analysis of GO and MGO, 1 ml of supernatant from the MDA preparation was mixed with 0.5 ml sodium acetate buffer (0.1 M, pH 3) and 0.5 ml of the derivatization solution (4- nitro-1,2-phenlenediamine in 1 % methanol). The mixture was incubated in a water bath for 30 min at 70 °C. Next, the derivatized sample was filtered using 0.45 μm cellulose acetate (CA) filter and injected into the HPLC.

HPLC analysis for the determination of GO and MGO was carried out as described previously with some modifications (Sahingoz Erdal et al., 2022). The HPLC equipment consisted of a Shimadzu LC 20 AT pump with a Shimadzu SPD-20 A UV/VIS detector (Shimadzu Corporation, Kyoto, Japan). The mobile phase consisted of methanol:water:acetonitrile (42:56:2 *v*/v/v). The wavelength of the detector was set to 254 nm. An Inertsil ODS-3 5 μ, 4.6 × 250 mm column was used for the separation. The flow rate was set at 1 ml/min and the column oven temperature was maintained at 30 °C.

2.3.2. Analysis of malondialdehyde

The analysis of MDA in plasma samples was carried out according to a method described previously (Aksoy et al., 2022) with some modifications. The MDA standard was generated by carrying out acid hydrolysis of tetraethoxypropane (TEP). Briefly, 0.1 ml of TEP was transferred into a 100 ml volumetric flask and the volume was completed with TCA (10 %, *w/v*). Next, the solution was incubated in a water bath at 35 °C for 2 h for the conversion of TEP to MDA. To determine the MDA levels in the plasma, 0.5 ml of the plasma sample was mixed with 2 ml of 10 % TCA in a 15 ml falcon tube. The mixture was centrifuged at 10,000 rpm for 5 min. Next, 1 ml of this supernatant was mixed with 1 ml of TBA solution (0.1675 g/250 ml) for derivatization. The mixture was placed in a water bath at 90 °C for 30 min. After cooling to room temperature, the derivatized sample was filtered using 0.45 μm CA filter and injected into the HPLC system.

A Shimadzu Nexera-i HPLC with a Shimadzu RF-20 A fluorescence detector (Shimadzu Corporation, Kyoto, Japan) was used for the detection of MDA. The mobile phase consisted of a mixture of 0.05 M KH_2PO_4 buffer solution:methanol:acetonitrile (72:17:11). The separation was carried out with a Gemini-NX 5 μ C18 110 A°, 4.6 mm × 250 mm column. The excitation and emission wavelengths of the fluorescence detector were set at 530 and 550 nm, respectively. The column oven temperature was set at 30 °C and flow rate was 1 ml/min.

2.4. Statistical analyses

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 software developed by IBM. The normality of the distribution was assessed using the Kolmogorov–Smirnov test. Accordingly, Mann-Whitney *U* test was used as a non-parametric test and Student's *t*-test was used as a parametric test for continuous variables. Pre- and post-treatment evaluations of GO, MGO, MDA levels and YMRS scores were analyzed with either paired samples t-test or Wilcoxon matched-pairs signed-rank test. The GO, MGO, and MDA levels were also compared separately between pre-treatment patients vs. healthy controls and post-treatment patients vs. healthy controls with the Mann-Whitney U test. Since BMI and waist circumference differed between the patients and healthy controls and were considered as potential confounders, one-way analysis of covariance (ANCOVA) was performed for comparisons between groups after adjusting for BMI and waist circumference. Either Pearson's or Spearman's correlation tests were used for exploring correlations between variables. The significance level was accepted as $p < 0.05$.

3. Results

Descriptive and clinical characteristics of the study sample are presented in Table 1. No significant difference in median age was observed between the patients and controls (29 (13) years and 27 (3.75) years, respectively; $Z = -0.747$, $p = 0.45$). The median number of years of education for the patient group (12 (7) years) was significantly lower than the control group (18 (2) years; $Z = -7.039$, $p < 0.01$). The average length of stay in hospital was 26.54 (9.05) days for the patient group.

BMI was significantly higher in the patient group compared to the healthy controls (26.6 (4.3) and 24.1 (6.8), respectively; $t = -2.004$, $p = 0.04$). Additionally, the waist circumference values were significantly higher in the patient group (92 (14.1) for patients and 85.5 (13.2) for the control group; $t = -2.100$, $p = 0.03$). Fasting glucose, high-density lipoprotein (HDL), triglyceride, BUN, creatinine, and estimated glomerular filtration rate (eGFR) levels did not differ between the patients and controls.

The levels of GO and MGO did not show any pre- and post-treatment difference in the patient group ($t = -1.156$, $p = 0.25$ and $Z = -0.579$, $p = 0.56$, respectively). However, a significant decrease was observed in MDA levels from pre-treatment to post-treatment ($Z = -3.615$, $p < 0.01$). As expected, YMRS scores significantly improved from pre-treatment to post-treatment (Table 2).

Binary analyses indicated that pre-treatment MGO and MDA levels were significantly higher in the patients than the control group ($Z = -2.644$, $p = 0.01$ and $Z = -6.474$, $p \leq 0.01$, respectively), while GO levels did not differ between pre-treatment patients and healthy controls. A

Table 1
Demographic and clinical variables of study participants.

	Patients ($n = 48$)	Controls ($n = 41$)		
	Mean (SD) / Median (IQR)		Test statistics	*p*
Age	29 (13)	27 (3.75)	Z = −0.747	0.45
Education (years)	12 (7)	18 (2)	Z = −7.039	**<0.01**
Age at illness onset	26.6 (9.8)	–		
Illness duration (years)	6.4 (6.8)	–		
Number of inpatient admissions (min-max)	3.4 (3.4) (1–19)	–		
Metabolic parameters				
BMI (kg/m^2)	26.6 (4.3)	24.1 (6.8)	t = −2.004	**0.04**
Waist circumference (cm)	92 (14.1)	85.5 (13.2)	t = −2.100	**0.03**
Fasting glucose (mg/dl)	86.4 (11.8)	83.6 (10.6)	*t* = −1.238	0.22
HDL (mg/dl)	40.5 (15.75)	39 (16)	Z = −0.101	0.92
Triglycerides (mg/dl)	107 (57.5)	124 (73)	Z = −1.245	0.21
Blood urea nitrogen (mg/dl)	24.7 (6.6)	24.5 (6.6)	*t* = −0.112	0.91
Creatinine (mg/dl)	0.82 (0.17)	0.82 (0.2)	Z = −0.372	0.71
eGFR	115.5 (20)	120 (18)	Z = −0.919	0.35
Smoking (pack-year)	3.5 (11.75)	3 (5)	Z = −1.269	0.20

Note: Z = Mann Whitney U test, t = independent samples t-test.
Abbreviations: SD = standart deviation, IQR = interquartile range,
BMI = body mass index HDL = high density lipoprotein.
eGFR = estimated glomerular filtration rate.

Table 2
Changes in RCCs levels and YMRS scores in the patients with treatment.

	Patients (n = 48)			
	At admission (T0-manic) Mean (SD) / Median (IQR)	**At discharge (T1-euthymic)** Mean (SD) / Median (IQR)	**Test statistics**	***p***
Glyoxal (mcg/ml)	0.054 (0.033)	0.060 (0.040)	t = −1.156	0.25
Methylglyoxal (mcg/ml)	0.049 (0.043)	0.040 (0.047)	Z = −0.579	0.56
Malondialdehyde (mcg/ml)	0.34 (0.43)	0.135 (0.178)	Z = −3.615	**<0.01**
YMRS	30.5 (9.25)	4 (2.75)	Z = −6.033	**<0.01**

Note: Z = Wilcoxon signed-rank test.
t = Paired samples *t*-test.
p: T0 vs T1.
$p < 0.05$ statistically significant.
Abbreviations: SD = standart deviation IQR = interquartile range.
AGE = Advanced glycation end products ALE = Advanced lipoxidation end products.
YMRS = Young Mania Rating Scale.

comparison of the markers between post-treatment patients and controls indicated that MGO and MDA levels remained significantly higher in the patients compared to the healthy controls (Z = -2.340, $p = 0.02$ and Z = -4.523, $p \leq 0.01$, respectively). The plasma GO levels did not differ between post-treatment patients and healthy controls (Table 3).

Clinical variables including age, age at illness onset, illness duration, number of inpatient admissions and YMRS scores did not show any significant correlation with carbonyl stress parameters (Table 4). Correlation analyses were carried out between the pre-treatment levels of metabolic variables (BMI, fasting glucose, creatinine, BUN, HDL, and triglyceride) and lifestyle factors (smoking) with pre-treatment carbonyl stress markers. We observed that BMI was significantly positively correlated with MGO ($r = 0.264$, $p = 0.016$), whereas waist circumference was significantly positively correlated with GO ($r = 0.278$, $p = 0.011$) and MGO ($r = 0.272$, $p = 0.013$).

Results from the binary analyses were further examined using ANCOVA to compare the levels of carbonyl stress markers between patients (both pre- and post-treatment levels) and healthy controls to examine the effects of confounders. For this analysis, the data were adjusted for BMI and waist circumference as potential confounders, since these variables differed between the patient and control groups. Our decision to adjust for BMI and waist circumference was also informed by prior research, as these factors have been suggested as indicators of obesity, which is known to increase peripheral AGE levels (van Waateringe et al., 2016). ANCOVA revealed that only MDA levels remained significantly higher in patients at both pre- and post-treatment stages compared to healthy controls (Table 5).

4. Discussion

The current study is the first to focus on carbonyl stress markers in BD by assessing the levels of GO, MGO, and MDA as RCCs. We compared the levels of these markers in patients at their drug-free pre-treatment manic episode as well as post-treatment euthymic phase with the levels determined in healthy controls. Our findings are important because we have excluded subjects with metabolic illnesses and the fact that, given their well-known effect on carbonyl stress, we considered metabolic markers such as BMI and waist circumference as potential confounders. The current study differs from previously published studies in the types of oxidative stress parameters evaluated in individuals with BD. Most previous findings have been inconsistent possibly due to variations in the parameters arising at different experimental stages in their measurement or differences across various patient groups, rather than focusing on the pre- and post-treatment phases of the same patients.

According to our binary analyses, MGO and MDA levels were higher in patients both at the manic pre-treatment and the euthymic post-treatment stages compared to the healthy controls. However, this difference remained significant only for MDA at both stages when the data were adjusted for BMI and waist circumference. Furthermore, MDA showed a significant decrease with treatment, while no significant change was observed in the levels of GO and MGO. These findings suggest that although MGO may be involved in the pathophysiology of BD, its levels may be influenced by metabolic parameters. However, it needs to be kept in mind that subjects with documented medical comorbidities or accompanying metabolic syndrome were excluded from the study. On the other hand, MDA stood out among the RCCs as the metabolite with the strongest association with the etiopathogenesis and clinical stage of BD.

Although the primary product of lipid peroxidation is lipid hydroperoxide, MDA is the most mutagenic of the aldehydes that can be generated as secondary products during lipid peroxidation. In comparison to reactive oxygen species, MDA possesses a relatively extended half-life, persisting from minutes to hours, which enhances its potential destructive effects. The longer half-life compared to other reactive oxygen species allows MDA to affect both cellular structures in proximity and macromolecular targets that are at a distance from the source of MDA (Jové et al., 2020). MDA levels showed a decrease in the post-treatment euthymic phase in the patients; nonetheless, it remained higher than the healthy controls. This may be attributed to the long half-life of MDA. This also suggests that neurotoxic effects of MDA may contribute to the pathophysiology of BD. MDA was proposed as a potential trait marker in a recent meta-analysis, which found elevated MDA levels even during euthymic states (Capuzzi et al., 2022). On the other hand, a significant decrease in MDA levels following the initiation of psychotropic medications has also been reported, which suggests an additional role for MDA as a state marker (Knorr et al., 2019).

Table 3
Comparisons of RCCs levels between pre-, and post-treatment stages for patients and controls.

	At admission (T0-manic) Median (IQR)	At discharge (T1-euthymic) Median (IQR)	Controls (n = 41) Median (IQR)	Test statistics	p^1	Test statistics	p^2
Glyoxal (mcg/ml)	0.054 (0.041)	0.054 (0.051)	0.048 (0.117)	Z = −0.609	0.54	Z = −0.082	0.93
Methylglyoxal (mcg/ml)	0.049 (0.043)	0.040 (0.047)	0.019 (0.043)	Z = −2.644	**0.01**	Z = −2.340	**0.02**
Malondialdehyde (mcg/ml)	0.34 (0.43)	0.135 (0.178)	0.064 (0.069)	Z = −6.474	**<0.01**	Z = −4.523	**<0.01**

Note: Z = Mann Whitney *U* test.
p^1: T0 vs control,
p^2: T1 vs control,
$p < 0.05$ statistically significant.
Abbreviations: IQR = interquartile range.

Combining these recent data with our study findings, we suggest that MDA could serve as a biomarker not only for the presence of BD but also for evaluating response to treatment. Such a biomarker has the potential to improve diagnosis and predict a patient's response to specific treatments.

MDA epitopes have demonstrated biological activity by triggering pro-inflammatory responses (Busch and Binder, 2017). These epitopes can be formed during tissue damage and stress, possess inflammation inducing properties and can be recognized by both immune and non-immune cells. This suggests that the epitopes can be classified as damage-associated molecular patterns that are a part of the innate immune response and can initiate inflammation (Busch and Binder, 2017). This is also consistent with a role of increased inflammation in the etiopathogenesis of BD. However, research into this relationship should consider factors that may potentially influence carbonyl stress, such as metabolic factors, as done in the current study. For instance, Tsai and Huang (2015) have investigated MDA in manic patients but did not exclude patients with metabolic syndrome. Moreover, lifestyle characteristics (such as smoking) and blood lipids were not considered in previous studies (Tsai and Huang, 2015). Lv et al. reported a decrease in MDA levels in manic patients before and after treatment in two separate studies. However, the sample size of the patients diagnosed with manic episodes in these studies was significantly smaller than the current study; additionally, these studies did not evaluate MDA levels together with confounders such as BMI and waist circumference (Lv et al., 2020, 2019). Moreover, consistent prior observations of higher levels of MDA in BD patients compared to the healthy population, as confirmed by a recent meta-analysis (Capuzzi et al., 2022), aligns with the findings of the current study.

The glyoxalase (GLO) enzyme system metabolizes GO and MGO and exhibits antioxidant properties. A role of RAGE has previously been assessed in mood disorders (Fujimoto et al., 2008). However, the current study is the first to determine the levels of these two molecules simultaneously. Previous animal studies have evaluated MGO levels alongside GLO function (Toriumi et al., 2022). Additionally, Fujimoto et al. (2008) observed a decrease in GLO1 mRNA expression in patients with major depressive disorder and BD with a depressive episode, although the study did not include patients undergoing a manic episode (Fujimoto et al., 2008). A comparison of AGEs, specifically pentosidine and carboxymethyl lysine, between BD patients at euthymia, manic, and depressive episodes with healthy controls indicated lower levels of AGE in individuals diagnosed with BD, contrary to expectations (Moutsatsou et al., 2014). This unexpected finding may be attributed to the relatively small sample size of the referred study. MGO is known to accumulate under conditions of hyperglycemia, impaired glucose metabolism, or oxidative stress and can react with proteins, DNA, and other biomolecules, contributing to the formation of AGEs (Hipkiss, 2017; Rabbani et al., 2016). Furthermore, AGEs formed by MGO can induce inflammation by binding to RAGEs, which has been associated with chronic inflammation and Alzheimer's disease (Blake et al., 2023). Several studies have implicated MGO as an etiological factor for dysfunctions in the metabolism of biogenic amines that are associated with mental and neurological conditions (Pignalosa et al., 2021). In line with this, MGO was shown to react with amine neurotransmitters such as dopamine and serotonin in vitro to form free radicals, and therefore may contribute to the pathophysiology of BD (Szent Gyorgyi and McLaughlin, 1975). We observed that MGO levels did not significantly change with treatment in the current study, but was still higher in patients during both the pre-treatment manic episode and post-treatment euthymic phase compared to healthy controls. However, this difference lost statistical significance when the data was adjusted for potential confounders such as BMI and waist circumference. These findings suggest that metabolic parameters are likely to have a substantial impact on MGO levels, even in the absence of established metabolic syndrome. Increased neurotoxicity and impaired cognitive functions observed in BD patients diagnosed with diabetes and metabolic syndrome may be associated with the higher levels of MGO in these patients, which therefore might mediate these effects (Bora et al., 2019; Lai et al., 2022).

In the current study GO did not show any significant difference between the control and patient groups, both in manic and euthymic stages, and even when the binary analysis was not adjusted for potential confounders. GO and MGO are structurally similar but can participate in different metabolic pathways (Yang et al., 2011). MGO is primarily detoxified by the GLO enzyme system, while GO can be converted to glycolate via the enzyme glyoxalase; however, no evidence for this reaction has been found in the scientific literature. Various carbonyl-metabolizing enzymes are involved in the detoxification of both GO and MGO. Differences in the activity of the detoxification systems could explain why GO was not found to be different in BD patients compared to healthy controls or the fact that its levels did not change with treatment. A decrease in the expression of the GLO-1 mRNA, which is known to play a role in the metabolism of MGO, has been previously reported (Fujimoto et al., 2008). This may explain the higher levels of MGO found in BD patients in the current study. In addition, MGO, unlike GO, can also be formed from the metabolite aminoacetone, which can be generated from the amino acids glycine and threonine (Vistoli et al., 2013). Such a distinction can partly shed light on the potential role of MGO, as opposed to GO, in the pathophysiology of BD, since the levels of MGO were significantly higher in the patients compared to healthy controls. However, comprehensive research is still needed to fully elucidate this.

We did not find any significant correlation between carbonyl stress parameters and clinical variables such as age, age at illness onset, illness duration, number of inpatient admissions and YMRS scores in the current study. It is worth noting that AGEs and ALEs are known to be higher in the elderly population (Twarda-clapa et al., 2022). Additionally, an association between the number of manic episodes and cumulative oxidative damage to lipids, proteins, and DNA has been reported (Soeiro-De-Souza et al., 2013). Conversely, studies carried out with early stages BD patients have also indicated an increase in oxidative and carbonyl stress (Magalhães et al., 2012). The relationship between YMRS scores and oxidative stress parameters reported in the literature has been inconsistent (Tsai and Huang, 2015). These contradictory findings suggest that carbonyl stress parameters are associated with the

Table 4
Correlation analyses for clinical variables and carbonyl stress parameters at baseline.

p / *r*	Age	Age at illness onset	Duration of illness	Number of inpatient admissions	YMRS	BMI	Waist circumference	Fasting glucose	Blood urea nitrogen	Creatinine	HDL	Triglycerides	Smoking (pack-year)
Glyoxal	−0.033	−0.169	0.007	0.012	−0.076[†]	0.130	0.278*[†]	−0.118[†]	0.06[†]	−0.058	0.157	−0.015	0.079
Methylglyoxal	0.157	0.135	−0.118	−0.158	−0.173	0.264*	0.272*	0.173	−0.018	−0.102	−0.028	−0.084	0.136
Malondialdehyde	0.005	−0.023	−0.040	0.083	0.197	0.094	0.075	0.076	0.056	0.115	−0.051	−0.070	0.041

Note: *r*: Pearson's correlation coefficient.
p: Spearman rank correlation coefficient.
Abbreviations
YMRS = Young Mania Rating Scale.
BMI = body mass index HDL = high density lipoprotein.
[†] Pearson correlation test.
* Correlation significant at 0.05.

Table 5
Adjusted RCCs levels for body mass index and waist circumference with ANCOVA and comparisons between pre-, and post-treatment stages for patients and controls.

	At admission (T0-manic) Mean ± SE	**At discharge (T1-euthymic)** Mean ± SE	**Controls (n = 41)** Mean ± SE	***p*[1]**	***p*[2]**
Glyoxal (mcg/ml)	0.053 ± 0.007	0.062 ± 0.007	0.067 ± 0.008[a] / 0.065 ± 0.009[b]	0.183	0.776
Methylglyoxal (mcg/ml)	0.055 ± 0.010	0.057 ± 0.110	0.040 ± 0.011[a] / 0.040 ± 0.013[b]	0.302	0.354
Malondialdehyde (mcg/ml)	0.562 ± 0.087	0.283 ± 0.049	0.092 ± 0.102[a] / 0.077 ± 0.057[b]	**0.001**	**0.009**

p^1: T0 vs control,
p^2: T1 vs control,
$p < 0.05$ statistically significant.
SE = standard error.
[a] mean ± SE for p^1.
[b] mean ± SE for p^2.

etiopathogenesis of BD rather than the severity or chronicity of the illness.

Careful consideration of possible confounding factors such as metabolic parameters, and the exclusion of comorbid metabolic illnesses, can be considered as the strengths of the current study, as these factors can potentially influence the formation of AGEs and ALEs. Furthermore, our results are reliable as the use of HPLC allowed for a more precise evaluation of RCCs. Despite these strengths, this study has several limitations. First, the current study had a small sample size, with recruitment limited to a single center. Although the study design included a prospective follow-up of the patient group, the evaluation of the control group in a cross-sectional manner due to the lack of opportunity for collection of a second blood sample from these subjects can be considered as an additional limitation. We only included male patients to maintain homogeneity and mitigate the potential effects of menstruation or pregnancy. However, this approach prevented us from assessing potential gender differences in the study outcomes. Finally, we did not analyze the effects of specific mood stabilizers or antipsychotic drugs that were administered to the patients. Additionally, blood samples were collected after treatment when patients had reached the defined euthymia criterion, which may have influenced the outcomes.

In conclusion, our study demonstrated that although both MGO and MDA levels were elevated in individuals diagnosed with BD compared to healthy controls, MDA could potentially serve as a biomarker for the diagnosis of BD and assessment of treatment response. On the other hand, MGO appeared to be influenced by the metabolic status of the patients, suggesting the presence of a potential link to increased neurotoxicity in patients with an adverse metabolic profile. The contributory role of RCCs to the pathophysiology of BD and their potential as markers of different mood episodes and clinical stages should be addressed in prospective cohorts with larger sample sizes and with the inclusion of female participants. New therapeutic strategies aimed at alleviating carbonyl stress by decreasing the synthesis of RCCs, as well as AGE and ALE, may pave the way for the development of new treatments for BD.

CRediT authorship contribution statement

Simge Seren Kirlioglu Balcioglu: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Imren Kurt Sabitay:**

Resources, Investigation. **Aybegum Uysal:** Resources, Investigation. **Esra Yildirim Servi:** Resources, Investigation. **Mustafa Yaman:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Omer Faruk Mizrak:** Resources, Investigation. **Nalan Ozturk:** Resources, Investigation. **Nilgun Isiksacan:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Oya Guclu:** Writing – review & editing, Resources, Investigation.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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