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## Ischemia-modified albumin: a unique marker of global metabolic risk in schizophrenia and mood disorders

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### ABSTRACT

**OBJECTIVE:** Conformational change in the last four amino acid of the albumin's N-terminus is called ischemia-modified albumin (IMA). Metabolic stress factors such as ischemia, hypoxia, acidosis or endothelial injury may cause these conformational modifications. In this study, we hypothesized that the plasma IMA level changes might help to determine the global metabolic risk in bipolar disorder (BD), unipolar depression (UD), and schizophrenia (SZ). Therefore, it was aimed to investigate metabolic risk factors affecting IMA levels in this study. Modification of the albumin molecule might be a marker of global metabolic risk in schizophrenia and mood disorders.

**METHOD:** The study included 32 patients with BD, 32 patients with UD, 28 patients with SZ and 34 healthy individuals. For determining the IMA levels, standard amounts of cobalt ions were added to the serums, and the quantity of disengaged cobalt ions was measured by colorimetric assay.

**RESULTS:** IMA ( $F = 3.04$ ,  $p = 0.032$ ) levels differed between the groups. IMA levels of the BD group were significantly higher than the healthy control group ( $p = 0.048$ ). White blood cell count in the BD group ( $p = 0.034$ ) and total oxidant status (TOS) in the SZ group ( $p < 0.001$ ) were the determinants of IMA levels with linear regression analysis.

**CONCLUSION:** Elevation of IMA levels may indicate a global metabolic risk, and IMA levels are elevated in the BD group in this study. Determinants of IMA levels may indicate the significant metabolic risk in patient groups. Oxidative stress (OS) was the determinant of IMA levels in the SZ, and white blood cell count was the determinant of IMA levels in the BD group. Although the IMA levels were higher in all patient groups, the statistical significance appeared only in the BD group. Elevated IMA level was due to elevated OS in the SZ group, whereas the immunity in the BD group.

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Ischemia-modified albumin; depression; bipolar disorder; schizophrenia

## Introduction

The average life expectancy in schizophrenia (SZ) and bipolar disorder (BD) is lower than that of the general population [1]. Cardiovascular and metabolic morbidity play an essential role in premature death in these populations [2]. There are many biochemical and metabolic concerns regarding the pathophysiology of SZ and mood disorders [3,4]. Metabolic issues mostly include metabolic syndrome, oxidative stress (OS), and defects in mitochondrial energy metabolism [5–7].

OS is one of the major metabolic problems, which occurs when redox homeostasis is reversed by the over-supply of free radicals, due to either their overproduction or deficiencies in antioxidant mechanism [8]. The resultant cellular damage may range from cellular structural damage and mitotic arrest to apoptosis and cell necrosis, depending on the level of OS severity [9]. Although free radicals are essential for numerous physiological functions, like mitosis and cellular

signalling, they can damage most of the contents of the cell if their metabolism is failed. This cell damage occurs by peroxidation of lipids, carboxylation of proteins and by the oxidative damage to the nucleic acids [10–12]. The cerebral tissue is particularly more vulnerable to oxidative damage due to relatively low levels of antioxidant defenses [13]. OS leads neurochemical and neuroanatomical changes and it is involved in many psychiatric and neurodegenerative diseases, such as SZ, BD, Alzheimer's, Parkinson's and Huntington's disease [12,14]. This vulnerability is mainly due to high levels of polyunsaturated fatty acids, high metal content and high oxygen utilization of the brain [15]. Therefore, an increase in the cerebral OS aggravates the endothelial damage which results in the degradation of vital cellular proteins [16,17].

Albumin is a protein, which acts as a binding molecule in the blood, and constitutes the majority of total blood protein concentration (50–60%) [18].

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Albumin binds other molecules in the blood and has an antioxidant and protective property [14,19,20]. It also contributes to oncotic balance between oncotic pressure or capillary permeability which is vital for the regular blood circulation [21]. The albumin molecule is composed of 585 amino acids and has a unique amino acid sequence specific to human species. The N-terminus of this unique amino acid sequence enables albumin to bind transitional metals (Co<sup>2+</sup>, Cu<sup>2+</sup>, Ni<sup>2+</sup>, Fe<sup>2+</sup>, etc.) [22,23]. Structure of the N-terminus is sensitive to biochemical stress, and it may easily be degraded and may abandon its metal-binding properties [24,25]. When N-terminus of albumin molecule becomes degraded, it is called as ischemia-modified albumin (IMA). The term “ischemia-modified” was used because hypoxia and acidosis were detected as the cause of degradation of the N-terminus [26,27]. In addition, IMA levels also increase in circulation rapidly following ischemia-reperfusion processes [25]. It has also been detected that degradation of the N-terminus is also caused by free radicals, dysfunction of sodium-calcium channels and high levels of free iron or copper ions [28,29]. OS is one of the reasons for degradation and conformational modification of the N-terminus of the albumin [30–32]. However, the IMA levels might be elevated with several metabolic risk factors other than high levels of OS, such as inflammatory activation, hypoxia, and obesity [33–37]. IMA is reported as an early marker for coronary artery disease, pulmonary embolism, the thromboembolic occlusion of superior mesenteric artery, acute stroke [38]. Higher IMA level is also reported in end stage renal disease, polytrauma, vascular and non-vascular surgery, obstetric conditions associated with placental ischemia as abnormal placental development, and ovarian torsion [32]. IMA is associated with cholesterol, low density lipoprotein (LDL), and antibodies to oxidised-LDL [32]. Type 2 diabetes mellitus (T2DM) patients with poor glycemic control have higher IMA concentrations than those with good glycemic control [32]. A high level of IMA is shown in carbon monoxide (CO)-poisoned patients, due to its sensitivity to hypoxia [38]. In this study, it was aimed to evaluate the relationship between OS, inflammation, and obesity with the advantage of IMA for their evaluation by assessing the blood IMA levels, and the determinants of IMA levels in the BD, UD, and SZ. In addition, we also aimed to evaluate determinants of IMA levels in these group of patients.

## Participants

This was a single centre, cross-sectional, a case–control study. Patients with BD type I and II ( $n = 32$ ), UD ( $n = 32$ ), and SZ ( $n = 28$ ) were enrolled into the study from the department of psychiatry outpatient clinic of the Kafkas University Faculty of Medicine in a consecutive

manner between the dates of November 2016 and March 2017. First-degree relatives of the hospitalized patients to surgery clinics participated in the study as the healthy controls (HCs) ( $n = 34$ ). The HC group was similar to the patient groups in terms of age, gender, and education. Healthy participants with a personal or family history of psychiatric disorders were excluded ( $n = 3$ ). All participants were initially evaluated by a clinical psychiatrist to confirm the appropriate diagnosis using the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) Axis I Disorders (SCID-I) [39,40]. The BD group was assessed with the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) [41–44]. The SZ group was assessed with the Scale for the Assessment of Positive Syndrome (SAPS) [45,46] and the Scale for the Assessment of Negative Syndrome (SANS) [47,48]. Exclusion criteria were substance and alcohol use disorders, accompanying psychiatric comorbidity as well as the cerebrovascular, cardiovascular, metabolic (Metabolic Syndrome, body mass index-BMI >35, cirrhosis, infections, and cancer) and the neurologic diseases. History of major physical trauma and other conditions which may elevate IMA levels, (i.e. exercise, minimal acidosis, obesity or slight dehydration) were the other exclusion criteria. Accordingly, 8 subjects (1 HC, 3 BD, 1 UD and 3 SZ) were excluded because their BMI were higher than 35; 1 patient with BD was in a manic episode, 2 patients had severe depression (1 BD and 1 UD); 5 subjects were alcohol users (2 HC, 2 BD and 1 UD) and 3 subjects had diabetes mellitus (1 HC and 2 BD). 4 subjects (1 HC, 1 BD, and 2 SZ) did not accept to be enrolled into the study. Clinically, manic patients (YMRS > 5) were excluded in the BD group, whereas mild to moderate depression (HDRS < 29) were allowed in the BD and UD groups [49]. No clinical exclusion was performed in the SZ group. A written informed consent was also provided by each participant after a full explanation of the study. The study was approved by the local Ethical Committee of the Kafkas University Medical School (26.10.2016, 80576354-050-99/106; Kars, Turkey) and was conducted according to the declaration of Helsinki.

## Biochemical analyses

The venous blood samples were left thirty minutes for coagulation after withdrawal and then centrifuged at 1500 G for fifteen minutes. All centrifuged samples were stored in Eppendorf tubes and kept frozen at  $-80^{\circ}\text{C}$  until the biochemical analyses have been performed. The serum albumin concentrations were measured by the bromocresol green (BCG) method. The IMA concentrations were measured as described by Bar-Or et al. [26]. This manual colorimetric assay measures the exogenous cobalt ( $\text{Co}^{2+}$ ) binding facility

of the human serum albumin. As described in this method, 50 µL water solution with % 0.1 cobalt chloride ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ) was gently mixed with 200 µL serum and kept dark for ten minutes. Then 50 µL of dithiothreitol (DTT) solution (1.5 mg/mL  $\text{H}_2\text{O}$ ) was added to the serum. After two minutes, 1.0 mL of 0.9% NaCl was added to trim the reaction. The blank was prepared similarly to the exclusion of DTT. The specimen absorbencies were assessed with a spectrophotometer at 470 nm. The IMA concentration was then obtained depending on the difference between the samples with and without DTT.

### Statistical analysis

Statistical analyses were performed with SPSS 22 software (IBM Incorporation, Armonk, New York, USA). Level of significance was 0.05 for *p* values. Variables were controlled for normality with Kolmogorov Smirnov Test. Categorical variables were compared with the Chi-Square Test, and continuous variables were compared with the *t*-test and one-way ANOVA. IMA and albumin levels were compared between groups with univariate ANCOVA. Levene's Homogeneity of Variances Test was performed and for homogeneous variances Bonferroni or Tukey Tests, for non-homogeneous variances Tamhane's Tests were performed. Pearson's Correlation Test was used to assess associations between clinical variables and IMA levels. For controlling the effect of albumin levels on the

relationship between IMA levels and other variables, Partial Correlation Analyses were performed. Determinants of IMA levels in the groups were investigated with stepwise Multiple Hierarchical Linear Regression Analysis. After checking the determinants in the first step, in the second step albumin levels was added as an independent variable. The change upon the new variable in the second step reflects the effect of the new variable on the relationship between the dependent and independent variables [50]. Level for statistical significance was 0.05 for *p* levels.

### Results

Sociodemographic and clinical variables of the groups are presented in Table 1. There was no significant difference between the groups regarding age, gender and education ( $p > 0.05$ ). There were differences between the groups in age at onset, duration of the disease, waist circumference, systolic and diastolic tension, number of hospitalizations and medications ( $p < 0.05$ , Table 1).

Comparison of the biochemical parameters is presented in Table 2. There was no significant difference between the groups in terms of albumin Total Antioxidant Status (TAS)/Total Oxidant Status (TOS) ratio ( $p > 0.05$ ). However, IMA ( $F = 3.04$ ,  $p = 0.032$ ) and TAS ( $F = 2.75$ ,  $p = 0.045$ ) levels differed between the groups. Post-hoc comparisons showed that IMA levels of the BD group were significantly higher than the

**Table 1.** Socio-demographic and clinical characteristics of the groups (BD: Bipolar Disorder, UD: Unipolar depression, SZ: Schizophrenia, HC: Healthy Control).

	BD ( <i>n</i> = 32)	UD ( <i>n</i> = 32)	SZ ( <i>n</i> = 28)	HC ( <i>n</i> = 34)	<i>F</i> / $\chi^2$	<i>p</i>
Age*	33.34 ± 1.13	33.91 ± 8.56	33.61 ± 10.02	30.62 ± 7.26	0.88	0.453
Gender [Women]	15 (%46.9)	16 (%50)	13 (%46.4)	20 (%58.8)	1.30	0.730
Education*	12.00 ± 3.30	11.84 ± 3.68	10.29 ± 3.93	12.59 ± 2.95	2.40	0.071
Age at Onset*	22.84 ± 7.46	29.38 ± 8.12	21.59 ± 3.96		6.01	<b>0.004</b>
Duration of the Disease**	109.00 ± 97.54	59.97 ± 59.27	140.78 ± 111.00		11.26	<b>&lt;0.001</b>
Waist Circumference	99.06 ± 11.83	93.00 ± 6.68	95.32 ± 10.83	89.35 ± 6.89	7.39	<b>0.001</b>
BMI	28.04 ± 5.05	25.07 ± 3.57	25.53 ± 5.62	24.56 ± 3.33	3.91	<b>0.011</b>
Systolic tension	120.47 ± 13.34	116.25 ± 11.07	112.14 ± 9.57	114.85 ± 11.51	2.77	<b>0.044</b>
Diastolic tension	77.34 ± 7.83	70.31 ± 7.06	70.00 ± 7.57	71.32 ± 8.82	6.03	<b>0.001</b>
Pulse rate	85.10 ± 12.64	74.03 ± 15.99	83.46 ± 18.70	78.18 ± 8.32	3.85	<b>0.010</b>
YMRS	1.45 ± 3.18					
HDRS	9.03 ± 9.07	10.71 ± 9.62				
SAPS			9.04 ± 9.56			
SANS			18.80 ± 17.52			
Number of Hospitalizations	3.10 ± 4.87	0.19 ± 0.64	1.71 ± 1.74		7.27	<b>0.001</b>
Number of Episodes					0.30	0.742
Depressive	2.46 ± 4.30	4.00 ± 1.41				
Manic	2.19 ± 3.93					
Total	7.54 ± 6.50					
Smokers (%)	13 (%40.6)	15 (%46.9)	10 (%35.7)	9 (%26.5)	3.14	0.370
Chlorpromazine Equivalents	317.27 ± 279.46	163.12 ± 207.57	347.41 ± 203.77		1.27	0.289
Drugs N (%)						
Antipsychotics <sup>‡</sup>	23 (%71.9)	7 (%21.9)	28 (%100)		75.73	<b>&lt;0.001</b>
Antidepressants	7 (%21.9)	31 (%96.9)	6 (%21.4)		76.93	<b>&lt;0.001</b>
Mood Stabilizers <sup>§</sup>	29 (%90.6)	2 (%6.3)	2 (%7.1)		92.63	<b>&lt;0.001</b>

One-way ANOVA and Chi-square Test. Post-hoc comparisons: Age at onset: BD < UD,  $p = 0.001$ , SZ < UD,  $p < 0.001$ ; Duration of the Disease: UD < SZ,  $p = 0.005$ ; Waist circumference: HC < BD,  $p = 0.001$ ; BMI: UD < BD,  $p = 0.010$ ; HC < BD,  $p = 0.042$  Number of hospitalizations: UD < BD,  $p = 0.007$ ; UD < SZ,  $p < 0.001$ ; Pulse rate, UD < BD,  $p = 0.020$ ; Systolic tension: SZ < BD,  $p = 0.041$ ; Diastolic tension: HC < BD,  $p = 0.027$ ; UD < BD,  $p = 0.002$ ; SZ < BD,  $p = 0.003$ . BD: Bipolar Disorder, UD: Unipolar depression, SZ: Schizophrenia, HC: Healthy Control.

\*Years.

\*\*Months.

<sup>‡</sup>2 patients in the BD group, 3 patients in the UD group and 5 patients in the SZ group were on typical antipsychotics.

<sup>§</sup>7 patients were on lithium, 14 patients were on valproate, and 8 patients were on lamotrigine in the BD group. 1 patient was on valproate, and 1 patient was on lamotrigine in the UD group. 1 patient was on valproate and 1 was on topiramate in the SZ group.

**Table 2.** Biochemical variables of the groups.

	BD (n = 32)	UD (n = 32)	SZ (n = 28)	HC (n = 34)	F / $\chi^2$	p
IMA	0.54 ± 0.16 (29.6%)	0.51 ± 0.14 (27.5%)	0.53 ± 0.15 (28.3%)	0.44 ± 0.09 (20.5%)	3.04	<b>0.032</b>
Albumin	3.99 ± 0.23 (5.8%)	3.93 ± 0.26 (6.6%)	3.87 ± 0.31 (8.0%)	3.93 ± 0.26 (6.6%)	1.21	0.311
TAS	1.42 ± 0.15 (10.6%)	1.44 ± 0.21 (14.6%)	1.45 ± 0.18 (12.4%)	1.33 ± 0.13 (9.8%)	2.75	<b>0.045</b>
TOS	4.40 ± 1.81 (41.1%)	3.66 ± 1.42 (38.8%)	3.83 ± 0.95 (24.8%)	3.47 ± 1.56 (45.0%)	2.33	0.077
TAS / TOS	0.38 ± 0.16 (42.1%)	0.43 ± 0.12 (27.9%)	0.40 ± 0.13 (32.5%)	0.46 ± 0.19 (41.3%)	1.46	0.228
Cholesterol	178.81 ± 44.78 (25.0%)	193.61 ± 36.89 (19.1%)	181.63 ± 31.29 (17.2%)	168.09 ± 34.01 (20.2%)	2.53	0.060
Triglyceride	128.84 ± 76.61 (59.5%)	150.00 ± 95.11 (63.4%)	154.00 ± 129.89 (84.3%)	125.30 ± 59.67 (47.6%)	0.749	0.525
WBC	6611.78 ± 2074.23 (31.4%)	7109.38 ± 2522.72 (35.5%)	7795.93 ± 2289.27 (29.4%)	7059.71 ± 1962.31 (27.8%)	1.41	0.244
Neutrophil	3832.53 ± 1502.41 (39.2%)	4132.53 ± 1509.33 (36.5%)	5204.04 ± 1699.19 (32.7%)	4323.28 ± 1574.98 (36.4%)	4.04	<b>0.009</b>
Lymphocyte	2198.88 ± 846.19 (38.5%)	2394.38 ± 1887.35 (78.8%)	2073.59 ± 603.88 (29.1%)	2259.59 ± 636.39 (28.2%)	0.40	0.750
Neutrophil / Lymphocyte	1.95 ± 1.03 (52.8%)	2.05 ± 1.05 (51.2%)	2.58 ± 0.72 (27.9%)	2.00 ± 0.80 (40.0%)	2.86	<b>0.040</b>
Hemoglobin	14.63 ± 1.80 (12.3%)	14.93 ± 1.56 (10.4%)	15.06 ± 1.46 (9.7%)	14.31 ± 1.48 (10.3%)	1.39	0.250
Hematocrit	43.19 ± 5.72 (13.2%)	44.25 ± 4.70 (10.6%)	44.78 ± 4.62 (10.3%)	41.92 ± 4.57 (10.9%)	2.05	0.111
Platelet	232.81 ± 91.18 (39.2%)	243.91 ± 76.02 (31.2%)	249.00 ± 58.90 (23.7%)	245.53 ± 71.54 (29.1%)	0.26	0.853

One-way ANOVA. Means ± SD (coefficient of variation %) are reported. Post-hoc comparisons: IMA: HC < BD,  $p = 0.048$ , HC < SZ,  $p = 0.059$ ; Neutrophil: BD < SZ,  $p = 0.007$  and Neutrophil / Lymphocyte ratio, BD < SZ,  $p = 0.045$ ; TAS was not significantly different between the groups in the post-hoc comparison. Partial eta-squared coefficient for IMA was 0.71, for TAS was 0.64, for neutrophil 0.92 and for neutrophil/lymphocyte 0.67. IMA: Ischemia-modified albumin, TAS: Total Antioxidant Status, TOS: Total Oxidant Status; WBC: White Blood Cell.

healthy control group ( $p = 0.048$ ). TAS levels did not differ between the groups in the post-hoc comparison. Neutrophil ( $F = 4.04$ ,  $p = 0.009$ ) counts and neutrophil/lymphocyte ( $F = 2.86$ ,  $p = 0.040$ ) ratio differed between the groups. Post-hoc comparisons showed that neutrophil counts of the BD group were significantly lower than the SZ group ( $p = 0.007$ ). In addition, Neutrophil/Lymphocyte ratio was higher in the SZ group in comparison to the BD group ( $p = 0.048$ ). Covariate analyses were performed with Univariate ANCOVA. Age, albumin, gender, nicotine consumption, BMI, chlorpromazine equivalents of antipsychotics, waist circumference, systolic, diastolic blood pressure, TAS, TOS, TAS/TOS ratio and other hematological and biochemical parameters were tested for covariance. BMI ( $F = 5.16$ ,  $p = 0.026$ ) and albumin levels ( $F = 4.04$ ,  $p = 0.048$ ) were the covariates of IMA levels. Nicotine consumption did not have an impact on IMA ( $t = -0.04$ ,  $p = 0.966$ ), TAS ( $t = 0.45$ ,  $p = 0.651$ ) and TOS ( $t = 1.06$ ,  $p = 0.285$ ) levels in all participants. There was no significant difference between smokers and non-smokers in groups (results are not reported).

Correlation analyses showed that IMA was positively correlated with BMI ( $r = 0.21$ ,  $p = 0.021$ ) in all groups. Albumin level was negatively correlated with the number of lymphocyte in all groups ( $r = -0.18$ ,  $p = 0.038$ ). Chlorpromazine equivalent doses of antipsychotics were positively correlated with albumin levels in all patient groups ( $r = 0.29$ ,  $p = 0.026$ ). In the BD group, IMA was negatively correlated with the number of lymphocytes ( $r = -0.38$ ,  $p = 0.030$ ), albumin level was positively correlated with the systolic blood pressure ( $r = 0.46$ ,  $p = 0.008$ ) and the diastolic blood pressure ( $r = 0.46$ ,  $p = 0.008$ ). In the UD group, IMA was positively correlated with the pulse rate ( $r = 0.37$ ,  $p = 0.037$ ), albumin level was negatively correlated with the number of lymphocytes ( $r = -0.35$ ,  $p = 0.031$ ). In the SZ group, IMA was positively correlated with TOS ( $r = 0.57$ ,  $p = 0.001$ ), albumin was

positively correlated with the hallucination subscore in SAPS ( $r = 0.39$ ,  $p = 0.040$ ). In the partial correlation analysis by correcting the IMA level according to the albumin level, IMA level was positively correlated with the sedimentation rate at the trend level ( $r = 0.37$ ,  $p = 0.068$ ) in the BD group. In the UD group, IMA was negatively correlated with TOS ( $r = -0.96$ ,  $p = 0.037$ ) and positively correlated with the TAS/TOS ratio ( $r = 0.99$ ,  $p = 0.007$ ). In the SZ group, IMA was positively correlated with TOS ( $r = 0.64$ ,  $p = 0.002$ ) and was negatively correlated with the TAS/TOS ratio ( $r = -0.41$ ,  $p = 0.063$ ). No other significant correlation was detected.

Predictors of IMA levels were analyzed with linear regression analysis in Table 3. White blood cell count in the BD group ( $p = 0.034$ ), pulse rate in the UD group ( $p = 0.040$ ), TOS in the SZ group ( $p < 0.001$ ) and systolic tension in the HC group ( $p = 0.018$ ) were the determinants of IMA levels.

## Discussion

In this study, there was a significant difference between the groups in terms of IMA levels. The BD group had significantly higher IMA levels in comparison to the HC group. The difference between the SZ and HC groups was at trend level. IMA levels were determined by WBC in the BD group ( $p = 0.034$ ), pulse rate in the UD group ( $p = 0.040$ ), TOS in the SZ group ( $p < 0.001$ ) and systolic tension in the HC group ( $p = 0.018$ ). Albumin levels interfered with the regression results in the hierarchical regression analyses.

Despite their essential functions in physiology, free radicals have the potential to damage all components of the cells, if their production exceeds the capacity of anti-oxidant systems [3,10]. Aggregation of oxidative damage is considered to cause neuronal death by apoptosis or because of the accumulation of oxidized proteins, which may lead to disruption of



**Table 3.** Predictors of IMA levels in the groups.

Model		Unstandardized coefficients		Standardized coefficients		t	p	F	Adjusted R <sup>2</sup>
		$\beta$	SE	$\beta$					
BD <sup>1</sup>	WBC	<0.001	<0.001	−0.43		−2.26	0.034	5.09	0.15
UD <sup>2</sup>	Pulse rate	0.003	0.002	0.39		2.16	0.040	4.67	0.12
SZ <sup>3</sup>	TOS	0.114	0.027	0.679		4.24	<0.001	17.97	0.44
HCS <sup>4</sup>	Systolic tension	−0.04	0.002	−0.46		−2.54	0.018	6.47	0.18

<sup>1</sup>Bipolar disorder.<sup>2</sup>Unipolar depression.<sup>3</sup>Schizophrenia.<sup>4</sup>Healthy controls.

Stepwise linear regression analyses were performed separately in the groups. Dependent variable: IMA; Independent variables: Waist circumference, BMI, Systolic tension, diastolic tension, pulse rate, cholesterol, triglyceride, TAS, TOS, TAS/TOS ratio, WBC, neutrophil, lymphocyte, Neutrophil/lymphocyte ratio. Albumin was added to the independent variables in the second step of the regression analysis to control the effect of albumin levels to IMA levels. In the second step regression models were not significant in all groups [BD  $F = 1.67$ ,  $p = 0.220$ ; UD  $F = 1.16$ ,  $p = 0.403$ ; SZ  $F = 1.43$ ,  $p = 0.327$ ; HCS  $F = 0.60$ ,  $p = 0.822$ ]. Second step analysis showed that significance in the first step depended on albumin levels in the groups.

mood stabilizing mechanisms [3]. Inflammatory and oxidative pathways are common metabolic risk factors for psychiatric disorders, and psychiatric disorders are incredibly co-morbid with cardiovascular disorders [3]. Life expectancy in schizophrenia and mood disorders is lower than the general population and lifestyle, and metabolic risk factors are among the most important causes of this reduced life expectancy [1,2]. The disequilibrium in the metabolic pathways causes metabolic diseases, like diabetes, atherosclerosis, hypertension, and obesity, and leads a major health problem worldwide [14]. Seriously increased prevalence of T2DM is reported in SZ, BD, and UD. Metabolic dysregulation, systemic inflammation, and OS have hypothesized as etiological mechanisms which are not entirely reciprocally [11]. Elevated OS is reported in T2DM and a marker of RNA damage from oxidation has been found as a prognostic marker for mortality in T2DM. Additionally, increased levels of DNA/RNA damage by OS have been found in SZ, BD, and major depression. Higher levels of systemic DNA damage from OS, assessed six years after the diagnosis of T2DM was found [11]. Metabolic risk factors can also cause neurotoxic processes by damaging cellular components in the brain and thus may aggravate poor prognosis in psychiatric disorders [12,13].

Albumin is the major serum protein and modification of albumin gives longitudinal information on metabolic stress exposure similar to hemoglobin-A1C (HgbA1c) [51]. Parameters associated with IMA levels in our study provide information on leading metabolic risk factors in diseases. Accordingly, OS in schizophrenia and immune system changes in bipolar disorder may be the leading cause of metabolic stress. Therefore, if albumin is a protein that plays an essential role in defense of antioxidants, its modification may be informative about the response of the body to OS [14]. The higher IMA levels are reported with vascular dysfunctions (cardiovascular complications, subclinical atherosclerosis) in  $\beta$ -thalassemia major ( $\beta$ -TM) as a marker of OS and hypoxia which are thought in the pathophysiology of thalassemia [31]. The higher IMA

levels are reported in diabetic patients. Higher IMA levels are shown with inadequate glycemic control compared to those with good glycemic control. The significant correlations between IMA and HgbA1c are reported. The significant correlations between IMA and total cholesterol, low-density lipoprotein (LDL) cholesterol, oxidized LDL antibodies and human serum-C reactive protein (hs-CRP) have also been shown. The formation of IMA is noted to be related with OS and atheromatous plaque development [38]. Hyperglycemia, hyperlipidemia, and inflammation via OS and chronic hypoxia might change albumin and impede its cobalt binding capacity, leading to higher IMA levels. The higher IMA levels are reported by long-duration exercise in marathon runners due to gastrointestinal ischemia or probably a delayed reaction to skeletal muscle ischemia, not because of myocardial or acute muscle ischemia at least in the immediate period after the exercise. It is important to identify higher IMA level is not reported in acute skeletal muscle ischemia or trauma unlike myoglobin [52]. It has been shown that albumin plays a role in the antioxidant defense in numerous ways. Plasma is a significant tool as a protective agent against oxidative damage to various blood components and also deploys dietary antioxidants to the remaining parts of the body. The antioxidant properties of albumin have been shown by numerous works. For example, serum albumin can neutralize hydroxyl radicals by reducing Cys34 [34]. Albumin not only can interfere with lipid peroxidation through binding copper ions but also works as sweeper of both oxygen and carbon-centered free radicals [39]. Albumin was also shown to be significantly lower in neuroleptic-naïve patients with first-episode SZ, which may be an indicator of immunological or acute phase protein response or OS [34,53]. Significantly lower albumin in chronic SZ patients may also be an indicator of OS [34,54]. The reduction in albumin level due to OS can be clarified by highly liver, and spleen uptake clearance than normal human serum albumin (HSA) and oxi-HSA that leaves the circulation quickly [34]. Modification of albumin may

also indicate the level of metabolic risk which exceeds the capacity of neutralizing mechanism. Furthermore, presence of different determinants of IMA levels between groups indicate that the major reason of metabolic risk differs between SZ and BD. Longitudinal studies may identify whether the IMA level might be utilized as monitoring global metabolic risk in psychiatric patients.





Small sample size and being a cross-sectional study were the major limitations of this study. There was a difference between the groups in terms of BMI. Acidosis, hypoxia, exposure to heat or cold are other factors that enhance IMA levels. Any markers of ischemia or pH change were not controlled in this study. External variables that may have affected our findings such as differences in diet, exercise, sleep were not controlled. As the course of SZ and BD include remissions and exacerbations, further studies should be performed to determine the changes in IMA levels during episodes. Moreover, since patients were on combination treatments, we were not able to analyze the potential effects of the medications.

To conclude, IMA levels were higher in BD, oxidative markers were the determinant of IMA levels in SZ, and immune markers were the determinant of IMA levels in BD. These findings may indicate that major metabolic risk is OS in SZ and immunity in BD. Further studies may investigate whether acute exacerbations of the disorders, obesity and medications may elevate IMA levels by causing a conformational modification in albumin. Longitudinal studies may examine whether IMA levels might be a prognostic marker or not.

## Disclosure Statement

No potential conflict of interest was reported by the authors.

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