Metabolic syndrome in bipolar disorder: prevalence, demographics and clinical correlates in individuals with bipolar I, bipolar II, and healthy controls

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Abstract

Background: The metabolic syndrome is a growing global public health problem and highly prevalent in patiens with bipolar disorder. There are a few studies about relationship between metabolic syndrome and bipolar disorder subtypes. **Objective:** The aim of this study was to investigate the prevalence of metabolic syndrome (MS) and its individual components in subjects with bipolar I (BD I) and bipolar II (BD II) disorder compared with non-psychiatric controls, and to determine the variables affecting MS. **Methods:** A total of 210 individuals (mean age 42.5 ± 11.87, 58.1% female) of whom 70 had BD I, 70 BD II, and 70 controls, were included in this study. MS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the adapted ATP III (ATP III-A) and the International Diabetes Federation (IDF) criteria. **Results:** Participants with BD I had a significantly higher prevalence of MS when compared to individuals BD II and non-psychiatric controls according to the NCEP-ATP III, ATP III-A, and IDF criteria (ps < 0.01). In individuals with MS, increased waist circumference was the most common abnormality. Logistic regression analysis revealed that the presence of physical illness, age and number of cigarettes smoked significantly predicted the presence of MS. **Discussion:** This study showed that MS was more prevalent among BD I individuals compared to BD II and controls, and highlighted the importance of regular screening for MS in individuals with BD.

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Introduction

Bipolar disorder (BD) is a chronic disorder that usually starts in adolescence and early adulthood, and is characterized by significant changes in the affective state and by impaired social and/or neuropsychological development[1]. According to the epidemiological field study in the United States of America (USA), the lifetime prevalence rate is 0.8% for bipolar I disorder (BD I), and 0.5% for bipolar II disorder (BD II)[2]. The World Health Organization (WHO) estimates that BD is currently the sixth leading cause of disability worldwide among adults. Depending on unhealthy lifestyle models such as high calorie diet, cholesterol intake, smoking and physical inactivity, 38% of individuals with BD suffer from cardiovascular disease (CVD). Life expectancy compared to the general population is 13.6 years shorter for male patients, and 12.1 years shorter for female patients[3]. In addition, the long-term use of some antipsychotics (AP) or mood stabilizers for treatment may be associated with an increased risk of developing obesity, dyslipidemia, diabetes mellitus, and metabolic syndrome (MS)[4].

MS leads to an increase in central obesity, fasting blood glucose (FBG), blood pressure (BP), and arteriosclerosis associated with deteriorating lipid profiles. Insulin resistance (IR) plays a role in its pathogenesis. It is becoming increasingly common all over the world. The risk of MS increases with age[5,6]. The prevalence of MS varies between 6% and 70%[7]. According to the results of the Metabolic Syndrome Research (METSAR) conducted across Turkey, the prevalence of MS was 35% among adults 20 years of age and over[8].

In studies conducted in different countries, it has been reported that the prevalence of MS in patients with BD varies between 22.4% and 67%[9-11]. Although there are not many studies undertaken on MS in Turkey, the prevalence of MS ranges from 24.7% to 36.7%[12,13]. It has been shown that unhealthy lifestyle habits (smoking, alcohol use, malnutrition, and lack of exercise) are frequently present in individuals with BD, and that these variables increase the risk for the development of MS. The relationship between BD and MS remained unchanged even after adjustments for age, race, smoking, physical inactivity, carbohydrate intake, and alcohol use[4]. Obesity is frequently associated with MS, and it is common among individuals with BD. In these patients, obesity has been associated with bad eating habits, lack of exercise, and the use of some psychotropic drugs leading to weight gain[14]. In obese people, the hypothalamic pituitary adrenal (HPA) axis may be disrupted due to increased leptin and other hormones released from the adipose tissue, which affects normal mood regulation, and consequently leads to significant and/or rapid mood fluctuations such as depression, mania, or the mixture of both mood states[15]. In individuals with BD, the presence of MS has also been found to be associated with a decrease in treatment response, a more adverse course of illness, increased frequency of manic and depressive episodes, and increased suicide tendency[16].

Therefore, in the current study, our first aim was to investigate the prevalence of MS in individuals with BD I, BD II, and non-psychiatric controls, and to compare patients with BD with the control subjects in terms of their demographics and clinical variables. The second aim of the study was to determine which of the individual MS components were associated with BD. We also aimed to identify the clinical correlates of MS in BD.

Methods

Participants

This study was carried out between 01.03.2016 and 01.07.2016 in the Department of Psychiatry at Tokat Gaziosmanpasa University Faculty of Medicine (Tokat, Turkey). A total of 210 subjects (age range: 18-65 years) consisting of 140 euthymic patients diagnosed with either BD I or BD II according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[17] and 70 non-psychiatric control

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subjects were enrolled in the study. The control group consisted of healthy volunteers who did not have any psychiatric diagnoses, and who presented to the outpatient clinic of the physical therapy department. Participants who suffered from comorbid alcohol- and drug-related disorders (except for smoking) were not included in the study (because of the low number of alcohol and substance users among the participants with BD during their remission period), and participants who had mental retardation (MR) and/or pervasive developmental disorders were excluded from the study.

Instruments of assessment

A demographic and clinical data form, which was prepared to assess the demographic and clinical features of the participants, was completed by the interviewer. Additionally, the Young Mania Rating Scale (YMRS)[18,19], the Bipolar Depression Rating Scale (BDRS)[20,21], the Beck Depression Inventory (BDI)[22,23] were used to assess the severity of the mood episodes of the participants. To calculate the amount of cigarettes smoked, we asked the participants how many packs of cigarettes they smoked daily and how many years they were smoking and the number of packs/year was recorded, the International Physical Activity Questionnaire Short Form (IPAQ-SF)[24] was used to assess the level of their physical activity. The Turkish versions of all these scales were used in the study[25].

Procedure

Face to face interviews were held with all of the participants. The questionnaires and scales used in the study were filled out by the interviewer, and the participants during these interviews. These questionnaires and scales were later rated by the interviewer. The groups (BD I, BD II, BD I+BD II, total participants) were divided into two groups: a) current cigarette smokers (yes = 1) and b) non-smokers (no = 0). Firstly the relationship between cigarettes smoking and the duration of illness was assessed. Secondly it was assessed whether there is a relationship between the amount of cigarettes and the duration of illness. Body weight, height, and waist circumference (WC) were measured to investigate the diagnostic criteria for MS in the participants and healthy controls. The participants also underwent blood tests to identify MS parameters. Biochemical findings [FBG, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG)], and BP measurements, which are examined routinely for MS, were recorded for all three groups. MS was diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the adapted ATP III (ATP III-A)[26,27], and the International Diabetes Federation (IDF)[28].

Statistical analyses

Independent samples' t-test, Pearson's chi-square and one-way analysis of variance (ANOVA) were used to determine whether there was a statistically significant difference between the means of the variables in the different groups. For group comparisions involving ANOVA, post-hoc Tukey analyses were performed to identify where the group differences were. Binary logistic regression analyses were used to assess the proposed relationship between the demographic and clinical variables and the presence of MS. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using a statistical software package (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Ethical approval

The study was approved by the Clinical Trials Ethics Committee of Tokat Gaziosmanpasa University Faculty of Medicine. The participants were also informed about the study. Then, written informed consent was obtained from the participants who voluntarily agreed to participate.

Results

Group comparisons according to demographic and clinical characteristics

A total of 210 participants (18-65 years) including 70 participants with BD I, 70 participants with BD II, and 70 non-psychiatric controls were enrolled in the study. The mean age was 43.51 (±11.75) years for the BD I group, 43.17 (±12.97) years for the BD II group, and 40.83 (±10.78) years for the control group. There was a significant difference among non-psychiatric controls and the other groups in terms of age ($p < 0.001$). The number of female participants in the BD II group was higher and there was a significant difference compared to the other groups ($p = 0.003$). Non-psychiatric controls were more successful in terms of work status than participants with BD ($p < 0.001$). The demographic characteristics of the participants are presented in Table 1.

The groups were compared with each other in terms of their clinical characteristics. In the BD I group YMRS score (± standard

Table 1. Demographic characteristics of the participants

Variables		Groups			χ^2/F	*p*
		BD I	BD II	Control		
Age (years)		43.51 (11.75)	43.17 (12.97)	40.83 (10.78)	11.773	< 0.001
Sex	Female	33 (47.1)	52 (74.3)	37 (52.9)	11.775	0.003
Marital status	Single	15 (21.4)	21 (30)	9 (12.9)	22.634	0.004
	Married	46 (65.7)	34 (48.6)	56 (80)		
	Divorced	7 (10)	6 (8.6)	4 (5.7)		
	Separated	2 (2.9)	3 (4.3)	0 (0)		
	Widow	0 (0)	6 (8.6)	1 (1.4)		
Level of education	Illiterate	2 (2.9)	6 (8.6)	1 (1.4)	22.420	0.013
	Primary school	33 (47.1)	21 (30)	21 (30)		
	Secondary school	9 (12.9)	10 (14.3)	3 (4.3)		
	High school	14 (20)	13 (18.6)	26 (37.1)		
	University	12 (17.1)	20 (28.6)	18 (25.7)		
Income level (TL)		974.54 (1021.73)	879.71 (1060.74)	1495.71 (951.60)	1.124	0.327
Employment *status*	Employed	29 (41.4)	22 (31.4)	53 (75.7)	30.212	< 0.001
Pack/year of cigarette smoking		5.75 (9.85)	3.94 (8.23)	3.53 (8.05)	2.156	0.118

Note. Results are presented as mean (standard deviation), or frequency (percentage). BD I: bipolar disorder I; BD II: bipolar disorder II; TL: Turkish Lira.

deviation (SD) was 0.26 (±0.97), BDRS score (±SD) was 3.1 (±3.05), BDI score (±SD) was 4.9 (±4.7), in the BD II group YMRS score (±SD) was 0.04 (± 0.36), BDRS score (±SD) was 3.5 (±3.03), BDI score (±SD) was 6.66 (±4.78), in the control group BDI score (±SD) was 4.9 (±4.7), and there was no significant difference between the groups in terms of these scale scores. The mean number of depressive episodes [± standard deviation (SD)], and the mean total number of mood episodes (±SD) were 4.94 (±2.48), and 8.66 (±3.69), respectively. In the BD II group, the mean number of depressive episodes (±SD), and the mean total number of mood episodes (±SD) were 5.49 (±2.67), and 8.67 (±4.27), respectively. There was a significant difference between the BD I group and the BD II group in terms of the mean number of depressive episodes, and mean total number of mood episodes (both p values 0.024). In the BD I group, the mean number of manic episodes (± SD), and the mean hypomanic episodes (± SD) were 3.0 (± 1.77), and 0.78 (± 1.48), in the BD II group, the mean hypomanic episodes 3.21 (±2.19 SD), respectively. The groups did not differ from each other on the mean number of manic/hypomanic episodes (p = 0.804). The cigarette smokers were twenty-one (30.%) participants for the BD I group, nineteen (27.1%) participants for the BD II group, and fourteen (20.%) participants for the control group. According to the results of statistical analysis, there was not found a significant relationship between smoking and duration of illness between groups (BD I (χ^2 = 0.258, df = 66, p = 0.79), BD II (χ^2 = 0.073, df = 68, p = 0.472), BD I+BD II (χ^2 = 0.320, df = 136, p = 0.50), total participants (χ^2 = 0.001, df = 208, p = 0.30). The mean amount of cigarettes (±SD) were 5.75 (±9.85) packs/year in the BD I group, 3.94 (±8.23) packs/year for the BD II group, and 3.53 (±8.05) packs/year for the control group, respectively. Additionaly, there was not a significant correlation between the amount of cigarettes and the duration of illness for BD I (correlation coefficient) r = 0.202, p = 0.094) and BD II (r = 0.151, p = 0.212). Mood stabilizers and combination therapies were significantly more frequently offered in the BD I group. There was a significant difference in the use of mood stabilizers and combination therapy (AP + mood stabilizers) between the BD I group and the BD II group (p = 0.002, p < 001).

Prevalence of metabolic syndrome and the presence of metabolic syndrome components according to the groups

In participants with BD who met the diagnostic criteria for MS, the prevalence of the individual diagnostic components was as follows: 93.4% for abnormal WC, 82.4% for low HDL, 74.7% for hypertriglyceridemia, 50.5% for high systolic BP, 48.4% for high FBG, 29.7% for high diastolic BP.

There was a statistically significant difference between the BD I group, and the BD II and control groups in terms of body mass index (BMI), WC, diastolic BP, triglycerides, and FGB (all p values < 0.001). On all these parameters, the BD I group had higher levels than the other two groups. On the same parameteres, there were no statistically significant differences between the BD II group and the non-psychiatric controls. Systolic BP was statistically significantly different between the BD I group and the non-psychiatric controls, and the BD I group had higher levels. There was a statistically significant difference in the HDL-cholesterol levels between the BD II group, and the non-psychiatric controls and the BD I group (p < 0.001), and the BD II group had higher levels than the other groups.

There was a statistically significant difference between the groups in terms of the prevalence of metabolic syndrome according to different diagnostic criteria (all p values < 0.01). According to the diagnostic criteria of the NCEP-ATP-III, the ATP-III-A, and the IDF, the prevalence of MS was higher in the BD I group than the BD II group and the non-psychiatric controls. The prevalence of MS did not differ from each other in the BD II group and the control group. Mean scores of the MS components and the prevalence of MS according to the groups are presented in Table 2.

Factors associated with metabolic syndrome

The effect of the independent variables sex (coded as female = 0/ male = 2), age, duration of psychiatric illness, presence of comorbid physical illness (coded as yes = 1/no = 2), total number of mood episodes, total number of hospitalizations, number of cigarette smoking (packs/year), total BDRS scores, and exercise status (MET (min/week (1 MET = 3,5 mL/kg/dk) on the presence of MS according to the IDF criteria was assessed by a binary logistic regression model. Because it was the most recent among other MS diagnostic criteria. There was a significant relationship between the presence of MS and the presence of comorbid physical illness, age, and the number of cigarettes smoked (p = 0.001, p = 0.037, p = 0.044, respectively).

Discussion

MS has also been known as Syndrome X, insulin resistance syndrome, Reaven syndrome, and the metabolic cardiovasculer syndrome[29]. MS was associated with a poor course of illness and prognosis in individuals with BD, suggesting that MS still is an important issue in clinical psychiatric practice[30,31].

In the present study, participants were assessed for MS according to the NCEP-ATP III, ATP III-A, and IDF criteria. According to the NCEP-ATP III criteria, the prevalence of MS was 57.1% for the

Table 2. Mean scores of the metabolic syndrome components according to the groups and prevalence of MS

	BD I		BD II		HC		χ^2	Post-hoc comparison	
	M	SD	M	SD	M	SD		(Tukey HSD)	*p*
BMI (kg/m²)	31.59	6.62	29.06	5.69	27.58	4.4	43.57	BD I>BD II=HC	< 0.001
WC	111.69	14.28	104.23	13.4	103.56	11.57	54.78	BD I>BD II=HC	< 0.001
Diastolic BP	79.43	8.49	75.21	8.18	76.71	9.59	18.56	BD I> BD II=HC	< 0.001
Systolic BP	124.14	13.13	121.0	11.05	118.49	14.74	21.07	BD I> HC=BD II	< 0.001
HDL-c	42.94	14.35	53.14	13.13	47.73	13.1	52.22	BD II>HC=BD I	< 0.001
TG	169.54	118.17	140.64	95.73	133.33	74.79	42.22	BD I>BD II=HC	< 0.001
FBG	110.53	49.26	96.83	24.07	93.57	17.96	13.48	BD I>BD II=HC	< 0.001
	BD I		BD II		HC		X^2		p
ATP-III	40 (57.1)		21 (30)		25 (35.7)		11.855		**0.003**
ATP-III-A	40 (57.1)		24 (34.3)		25 (35,7)		9.399		**0.009**
IDF	41 (58.6)		24 (34.3)		26 (37.1)		10.045		**0.007**

BD I: bipolar disorder I; BD II: bipolar disorder II; HC: healthy control subjects; M: mean score; SD: standard deviation; F: one-way ANOVA; HSD: highly significant difference; BMI: body mass index; WC: waist circumference BP: blood pressure; HDL-c: high-density lipoprptein; TG: triglycerides; FBG: fasting plasma glucose; ATP-III: National Cholesterol Education Program Adult Treatment Panel; IDF: Internal Diabetes Federation.

BD I group, 30% for the BD II group, 35.7% for the non-psychiatric controls, according to the ATP III-A criteria 57.1% for the BD I group, 34.3% for the BD II group, 35.7% for the non-psychiatric controls and according to the IDF criteria 58.6% for the BD I group, 34.3% for the BD II group, 37.1% for the non-psychiatric controls. According results of previous MS prevalence in participants with BD studies, MS prevalence ranged from 17% to 53%[27,32-34]. MS prevalence has been reported to be 18-26% in European countries[10,35,36], and 30-49% in the USA[4,36-38]. The lower prevalence rate in European countries has been attributed to differing eating habits, ethnicity, and lifestyle[4]. The studies we use in relation to MS prevalence are presented in Table 4.

Focusing specifically on studies of MS in BD, in a study conducted in Taiwan where the participants with BD I (n = 15), BD II (n = 16), major depressive disorder (MDD) (n = 141), and anxiety disorders (n = 36) were compared in terms of the prevalence of MS, it was reported that 46.7% BD I, 25% BD II, 22% MDD, and 18.4% anxiety disorder participants suffered from MS[34]. In another study, which was conducted in New Zealand, the prevalence of MS was reported to be 50% for participants with BD, and 32% for healthy controls[16]. In a study in which participants with BD II without treatment (valproate acid and fluoxetine were used if needed) were monitored for 12 weeks in terms of their MS parameters, it was reported that only the BMI increased during the observation period. Therefore, the authors concluded that BD II was more moderate in terms of metabolic dysregulation, and that the prevalence of MS in BD II was similar to the general population[35]. In our study, the prevalence of MS was lower in the BD II group and the non-psychiatric controls than in the BD I group.

Not many studies were conducted in Turkey in this area of research, and in one of these studies, which consisted of 125 participants, the prevalence of MS was reported 32%[8]. In another study, evaluating the efficacy of agents used for MS treatment in BD, 60 participants were reported to have MS, with a prevalence rate of 36.7%[13]. We obtained a higher MS prevalence for BD I participants

Table 3. Summary of logistic regression analysis predicting the diagnosis of metabolic syndrome

	B	S.E.	OR	95 % CI	Wald	*p*
Sex	-.357	0.405	0.70	[0.317, 1.546]	0.77	0.37
Age (years)	-.038	.018	0.963	[0.929, 0.998]	4.33	**0.037**
Disorder duration (years)	0.004	0.026	1.004	[0.954, 1.056]	0.019	0.89
Presence of comorbid medical disorder	-1.572	0.474	0.208	[0.082, 0.526]	10.98	**0.001**
Total number of depressive episodes	0.051	0.099	1.052	[0.867, 1.277]	0.267	0.605
Total number of manic episodes	-0.253	0.191	0.776	[0.533, 1.130]	1.746	0.186
Total number of hypomanic episodes	-0.036	0.109	0.985	[0.779, 1.196]	0.106	0.745
Total number of hospitalizations	-0.002	0.201	0.998	[0.673, 1.479]	0.00	0.991
Exercise status (MET)	-0.169	0.494	0.844	[0.321, 2.222]	0.117	0.732
Number of cigarettes smoked (packs/year)	0.083BB	0.040	0.920	[0.850, 0.996]	4.248	**0.039**
BDRS total score	0.124	0.084	1.132	[0.961, 1.335]	2.195	0.138
BD I	-0.358	1.123	0.699	[0.077, 6.321]	0.101	0.750
BD II	-0.280	1.081	0.756	[0.091, 6.287]	0.067	0.796

Note: Comorbid medical disorder (1: yes, 2: no), Exercise status [1: 600-3000 MET (min/week (1 MET = 3,5 mL/kg/dk)], 2: > 3000 MET min/week). BD I: bipolar disorder I; BD II: bipolar disorder II; BDRS: Bipolar Depression Rating Scale.

Table 4. Summary of studies documenting the rate of metabolic syndrome in bipolar disorder

Author/year	Sample size		Location MS	MS Definition	Rate of MS	Rate of general population
Fagiolini *et al.* (2005)	171 BD, BD I-71%, BD II-26%, BD NOS-3%		USA	NCEP-III	30%	23.7%
Cardenas *et al.* (2008)	98 BD I/II		USA	NCEP-III	49%	
Birkenaes *et al.* (2006)	103 Sch, 83 BD I/II		Norway	NCEP-III	30%	
Fiedorowicz *et al.* (2008)	60 BD, BD I-59%, BD II-34%, BD NOS-7%		USA	NCEP-III	50%	27.3%
Sicras *et al.* (2008)	178 BD		Spain	NCEP-III	24.7%	14.4%
Yumru *et al.* (2007)	125 BD I		Turkey	NCEP-III	32%	
Salvi *et al.* (2008)	99 BD		Italy	NCEP-III and IDF 30% (IDF)	25.3% (NCEP-III),	16-17.8%
Correl *et al.* (2008)	74 BD		USA	NCEP-III	43.2%	23.7%
Garcia-Portilla *et al.* (2008)	194 BD		Spain	NCEP-III	22.4%	17.9%
Elmslie *et al.* (2009)	60 BD and 60 Controlled		New Zealand	NCEP-III	BD 50%	
	BD I-40,BD II-18, BD NOS-2				Control 32%	
Chang *et al.* (2009)	117 BD		Taiwan	IDF 2005	33.9%	M-20.4%, F-15.3%
van Winkel, de Hert (2008)	60 BD		Belgium	NCEP-III, Adapted NCEP III	16.7% (NCEP-III)	
				IDF	18.3% (adapted)	
					30.0% (IDF)	
	BD I	BD II		Cyclothymia	Hypomania	
Prevalence of BD (Lifetime)	0.2-4	0.3-4.8		0.5-6.3	2.6-7.8	

NCEP-III: National Cholesterol Education Program Adult Treatment Protocol; IDF: International Diabetes Federation, BD: bipolar disorder.

in our study. Previous studies have reported that the use of lithium, valproic acid and atypical antipsychotics (e.g. olanzapine, clozapine) contributed to obesity and MS in the BD group, mainly due to their effects on appetite and glucose and lipid metabolism[32,39]. The higher prevalence of MS in BD I group in our study may be related to the higher use of AP and mood stabilizers in this group. It also differs from other studies since BD II participants and non-psychiatric controls were also included. Although this finding may have been somewhat affected by the geographic differences, these differences might also indicate that additional factors, including genetic vulnerability and environmental (lifestyle) effects, may have played a role in modifying MS prevalence rates in patients with BD[33]. At this point, it should be emphasized that abdominal obesity is one of the main causes for the occurence of all the components of MS, because adipose tissue plays an important role in lipid and glucose metabolism, and because it is responsible for the production of various cytokines influencing the development of the syndrome[40]. In studies evaluating the prevalence of obesity in Turkey, the prevalence was reported 25 % in Trabzon[41], 28% in Ankara[42] and Kocaeli[43], and 29% in Mersin[44]. The prevalence of obesity in Tokat was higher than these cities, and it was reported 33.6 % for women, and 12.9 % for men[45]. Therefore, the difference of MS prevalence reported in these studies may be due to the differences in the prevalence of obesity, which is the major component of MS in the general population.

According to the IDF criteria, the prevalence of MS was 58.6% for the BD I group, 43.3% for the BD II group, and 37.1% for the non-psychiatric controls. In a study that investigated the prevalence of MS with different diagnostic criteria in participants with BD, it was determined that the prevalence of MS was 25.3% according to the ATP-III criteria, and 30% according to the IDF criteria[4]. Similarly, a higher prevalence of MS was detected with the IDF diagnostic criteria in our study.

The mean values for WC, BMI, systolic BP, diastolic BP, FBG, and TG levels were found to be higher in the BD I group compared to the BD II group and the control group. These values were similar in the BD II group and the control group, there was no significant difference between these two groups. In a recent study that compared participants with BD with participants with MDD and non-psychiatric controls in terms of MS parameters, it was reported that the mean values of WC, triglycerides, systolic BP, diastolic BP, and FBG levels were higher in participants with BD than in participants with MDD and in non-psychiatric controls, and there were also differences between the MDD group and the control subjects, where the levels were higher in the MDD patients than in the non-psychiatric controls[46]. Our study compared euthymic participants with BD I and BD II with non-psychiatric controls, which differs from other studies. Hence, these results are a novel addition to the literature.

In our study, the mean HDL-cholesterol levels were found to be the highest for the BD II group, and the lowest for the BD I group. These findings were in line with the prevalence of MS in our study. In a study that compared participants with BD with participants with MDD and non-psychiatric controls in terms of their HDL-cholesterol levels, the mean HDL-cholesterol levels were significantly the highest in non-psychiatric controls and was the lowest in BD I. In this study, an inverse relationship was found between the HDL-cholesterol levels and MS prevalence, which was similar to our findings[46]. Therefore it may be hypothesized that in patients with BD, HDL-cholesterol levels are a predictor for MS frequency, but surely there is a need for further studies to confirm this finding.

When analysing the prevalence of each of the components of MS in our population, we found that increased WC was the most common abnormality (93.4%), followed by abnormalities in low HDL-cholesterol levels (82.4%), increased triglyceride levels (74.7%), increased systolic BP measurements (50.5%), increased FBG (48.4%) levels, and increased diastolic BP measurements (29.7%). The majority of studies undertaken in participants with BD indicate that increased WC was the most[9,10,38,47-49], and increased FBG was the least frequently encountered abnormality[4,10,38,47,49-52], and our findings are also, to a great extent, in line with these previous reports.

Daily exercise time was found to be lower in the BD I group compared to the BD II group and the control group. In a study that examined the relationship between eating and lifestyle habits and metabolic disorders in participants with BD, unhealthy eating habits and lack of exercise were found to be higher in participants with BD than in healthy participants. In the same study, it was reported that unhealthy eating habits and lack of exercise were associated with weight gain and obesity[53].

Additionaly, relationship between participants smoking behavior and duration of illness was examined; there was not found a significant relationship between smoking and duration of illness and there was not a significant correlation between the amount of cigarettes and the duration of illness in our study. However, Medeiros *et al*., found a significant relationship between smoking and duration of illness, severity of manic symptoms in bipolar subjects[54]. Our study results were different, this discrepancy can be related to the fact that participants were in clinical remission.

The participants were assessed in terms of variables affecting MS, and there was a significant relationship between MS and the presence of comorbid physical illness, age and number of cigarettes smoked. The diagnostic categories of BD I or BD II were not associated with the presence of MS. In a study involving participants with BD I and BD II in which factors affecting the development of MS were assessed, it was reported that there was a relationship between the development of MS and age, BD I diagnosis, use of AP or mood stabilizers[55]. Our results are very similar to those reported by Van Winkel *et al*., in which patients with BD and MS were older than those without[36]. Aging is commonly accompanied by a loss of muscle mass and by an increase in body fat, especially in the abdomen, and both of these changes can increase IR and finally lead to MS[28]. Additionally, the meta-analysis by Sun, Liu and Ning[56], based on data from prospective studies concluded that active smoking was associated with the development of MS. In another study that examined the relationship between smoking and metabolic disorders, it was reported that smoking was higher in patients diagnosed with MS[57]. On the other hand, another study reported that there was no relationship between MS and smoking[4]. The results of our study add to the literature that there might be a significant relationship between MS and smoking.

The findings of the current study suggest that active and early screening of metabolic parameters, including triglycerides, and HDL-C levels, WC measurements, and lifestyle interventions, including dietary changes and physical activity are absolutely essential to managing MS among patients with BD and the general population. The Mediterranean diet (MD) is a dietary pattern first presented by Ancel Keys in the 1960s[58], and it is characterized by a high intake of fruits, vegetables, legumes, fish, whole grains, nuts, and olive oil; moderate consumption of dairy products and wine; and low intake of red and processed meats and foods that contain high amounts of added sugars[59]. The beneficial role of the MD with regard to mortality from all causes, cardiovascular disease (CVD) and cancer, as well as obesity and type 2 diabetes[60,61] has already been reported from the results of many epidemiological studies and clinical trials. Similar recommendations should proactively be pursued for the physical health status of patients with BD, and a closer follow-up regarding the metabolic parameters should be part of their routine clinical management program.

When the results of the current study are evaluated, it is necessary to consider the limitations of the study. The fact that participants were evaluated cross-sectionally, and that they were not followed up longitudinally, and that all of the patients were in an euthymic period might limit the generalizability of the results. Other limitations of the study are (i) there was no definitive causal relationship in the outcomes, (ii) the study results could not be compared, or were only suboptimally compared, with other studies in the literature due to lack of similarly designed studies in similar clinical populations, (iii) it was not possible to compare the groups which were offered psychopharmacological treatment with those who were not, which

might be a contributing factor for the development of MS, and (iv) did not evaluate the role of comorbid alcohol and substance use.

In light of the high rates of MS observed in all settings, we propose that minimum monitoring for all individuals, even those with normal baseline tests, should include WC or BMI at these time points. Optimal monitoring should also include assessments of FBG, triglycerides, HDL-c and BP. Patients treated with drugs with potential for weight gain and metabolic side effects should be evaluated more frequently in terms of weight and metabolic parameters. For the medical treatment of MS, lifestyle changes such as weight loss, regular exercise, smoking cessation, healty eating are also important. The MD is one of the healthiest dietary patterns, and it may help with the prevention and treatment of cardiovascular disase, diabetes, hypertension and MS.

In conclusion, this article aimed to draw attention to MS, which not only affects patients with BD, but also increases in frequency in healthy individuals all over the world, and to emphasize the importance of necessary measures to be taken. BD is relatively highly comorbid with MS, and appropriate interventions should be prioritized against the development of MS in BD.

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