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ORIGINAL ARTICLE

Atherogenic index of plasma as a cardiovascular risk marker in manic, depressive, and euthymic stages of bipolar disorder

Bipolar bozukluğun manik, depresif ve ötimik evrelerinde bir kardiyovasküler risk belirleyicisi olarak aterojenik plazma indeksi

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ABSTRACT

Objective: Individuals with bipolar disorder (BD) frequently suffer from cardiovascular disease (CVD), and it is a leading cause of mortality. Clinicians use routine laboratory tests, including a lipid profile, to predict cardiovascular risk. In addition, a particular lipid ratio, the atherogenic index of plasma (AIP), is a sensitive, new parameter that can be used to assess high-risk groups. To our knowledge, this is the first study evaluating cardiovascular risk via AIP in different stages of BD.

Methods: The study group consisted of male patients with BD who were in a manic, depressive, or euthymic state, and age- and gender-matched healthy controls. Lipid profiles were analyzed and the AIP parameter of logarithm of triglyceride (TG) / high-density lipoprotein cholesterol (HDLc) was calculated for all of the participants. The significance level was set at $p<0.05$.

Results: A total of 44 BD patients experiencing a manic episode, 35 depressive BD patients, 42 euthymic patients, and 41 healthy controls matched for age, gender, and smoking status were enrolled in the study. The AIP level was significantly different between groups ($p=0.009$). Pairwise comparisons of the groups revealed that the AIP level of depressive patients was significantly higher than that of the manic, euthymic, and control groups ($p=0.013$, $p=0.048$, and $p=0.021$, respectively). The AIP level was positively correlated with body mass index, waist circumference, metabolic syndrome, total cholesterol, low-density lipoprotein, and triglyceride level, and was negatively correlated with the HDLc level.

Conclusion: In this study, male BD patients in a depressive episode demonstrated an increase in cardiovascular risk. The significant correlations between AIP and other conventional cardiovascular risk factors indicate that AIP may be more useful to identify individuals with BD at high risk for CVD than absolute lipid parameters.

ÖZET

Amaç: Bipolar bozukluğu (BB) olan bireylerde, mortalitenin başlıca nedeni olan kardiyovasküler hastalıklar sıkça görülmektedir. Klinikçiler kardiyovasküler riski öngörmek için lipit profili de dahil olmak üzere rutin laboratuvar testlerini kullanmaktadırlar. Rutin testlerin yanında, lipit parametrelerinin çeşitli oranlamalarıyla hesaplanan aterojenik plazma indeksi (APİ) de, yüksek riskli grupları değerlendirmek için kullanılan yeni ve hassas bir parametredir. Bildiğimiz kadarıyla çalışmamız bipolar bozukluğun farklı evrelerinde APİ yoluyla kardiyovasküler riski değerlendiren ilk çalışmadır.

Yöntemler: Çalışmamızın grupları, BB tanılı ve manik, depresif veya ötimik dönemde olan hastalar ile yaş-cinsiyet eşleştirilmiş sağlıklı kontrollerden oluşmaktadır. Tüm katılımcılar için lipit profili incelendi ve APİ log (TG / HDLc) parametresi hesaplandı. Anlamlılık düzeyi $p<0.05$ olarak belirlendi.

Bulgular: Manik atakta olan 44, depresif dönemde 35, ötimik dönemde 42 BB'li hasta ve yaş, cinsiyet ve sigara içme durumu eşleştirilmiş 41 sağlıklı bireyden oluşan kontrol grubu çalışmaya alındı. APİ düzeyleri gruplar arasında anlamlı fark gösterdi ($p=0.009$). Grupların ikili karşılaştırmalarında, depresif hastaların APİ düzeyi manik, ötimik ve kontrol gruplarına göre anlamlı derecede yüksekti (sırasıyla, $p=0.013$, $p=0.048$ ve $p=0.021$). APİ düzeyleri vücut kitle indeksi, bel çevresi, metabolik sendrom varlığı, toplam kolesterol, düşük yoğunluklu lipoprotein, trigliserit düzeyleri ile pozitif yönde ve yüksek yoğunluklu lipoprotein düzeyi ile negatif korelasyon gösterdi.

Sonuç: Çalışmamızda depresif dönemdeki BB'li hastalarda kardiyovasküler risk artışı saptandı. APİ'nin diğer geleneksel kardiyovasküler risk faktörleri ile anlamlı korelasyon göstermesi, yüksek riskli BB'li bireyleri tanımlamak için APİ'nin lipit parametrelerinin tek tek ölçülmelerinden daha yararlı olabileceğini göstermektedir.

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The risk for cardiovascular disease (CVD) has been observed to be 5-fold higher in patients with bipolar disorder (BD) than in the general population. The increased and premature manifestation of CVD mortality in BD patients was documented before the use of psychotropic medication, suggesting that the illness itself contributes to cardiovascular risk.[1] Atherogenic index of plasma (AIP) is a marker that can be used to predict cardiovascular risk. AIP is obtained from 2 important lipid parameters: triglyceride (TG) and high-density lipoprotein cholesterol (HDLc) levels. Calculated using the formula of logarithm (TG/HDLc), it has been suggested that an AIP value between -0.3 and 0.1 is associated with a low cardiovascular risk, a value of between 0.1 and 0.24 with a medium risk, and a value greater than 0.24 with a high cardiovascular risk.[2]

The aim of the current study was to evaluate the cardiovascular risk during the manic, depressive, and euthymic stages of BD, and to see if this measure could be used to predict the groups at high cardiovascular risk.

Abbreviations:

AIP	*Atherogenic index of plasma*
BD	*Bipolar disorder*
BMI	*Body mass index*
CVD	*Cardiovascular disease*
HDLc	*High- density lipoprotein cholesterol*
HDRS	*Hamilton Depression Rating Scale*
HPA	*Hypothalamic-pituitary-adrenal*
LDLc	*Low-density lipoprotein cholesterol*
MDD	*Major depressive disorder*
TG	*Triglyceride*
YMSR	*Young Mania Rating Scale*

METHODS

Participants

Male, hospitalized BD patients experiencing a manic episode, depressive BD inpatients and outpatients, and euthymic outpatients, identified according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, were enrolled in the study. The Young Mania Rating Scale (YMRS) was used to evaluate the severity of mania. Bipolar depression was assessed with the 17-item Hamilton Depression Rating Scale (HAM-D). A HAM-D severity score ≥20 was required for BD depressive group inclusion. A euthymic state was defined as YMRS ≤7 and HAM-D score ≤7.[3] Additionally, healthy controls matched for age, gender, and smoking status were enrolled in the study. All of the participants were between the ages of 18 and 65 years. The exclusion criteria were any psychiatric comorbidity, the presence of mental retardation, alcohol and/or substance abuse, and any acute infectious disorder. Blood samples were drawn in the morning from a forearm vein following an overnight fasting period. A complete biochemical evaluation and a hemogram were performed for all members of the study group. Metabolic syndrome was evaluated according to the National Cholesterol Education Program Adult Treatment Panel III criteria. The presence of 3 of the following was diagnosed as metabolic syndrome: waist circumference ≥102 cm (≥40 in), blood pressure of systolic ≥130 mmHg and diastolic ≥85 mmHg, HDLc <40 mg/dL (1.04 mmol/L), TG of ≥150 mg/dL (1.7 mmol/L), and a fasting glucose ≥110 mg/dL (6.1 mmol/L). This study was approved by the Bakırköy Mental Health Research and Teaching Hospital ethics committee, and all participants and their legal representatives gave written informed consent before enrollment.

Statistics

The continuous variables were expressed as mean±SD and the categorical variables were reported as number (n) and percentage (%). A chi-square test was used to compare categorical variables. The Kolmogorov-Smirnov test was performed to assess the normality of the distribution. The Kruskal-Wallis test or analysis of variance with Tukey's post-hoc analysis was used to compare the continuous variables between groups. For pairwise group comparison, the Mann Whitney-U test was performed for non-parametric data. Spearman's correlation test was used to determine the linear associations between variables. An analysis of covariance (ANCOVA) test was used to correct for age, body mass index (BMI), smoking status, and drug medication. The level of significance was $p<0.05$. The data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 44 BD patients experiencing a manic episode, 35 depressed BD patients, 42 euthymic patients, and 41 controls matched for age, gender, and smoking status were enrolled in the study. The mean age of the manic patients was 38.22±11.37 years and in the depressive group it was 41.54±10.29 years. For the euthymic patients, the mean age was 40.52±10.90

years, and it was 39.02±10.69 years for the healthy group (p=0.530). The duration of illness for the manic, depressive, and euthymic patients was 11.65±9.42 years, 17.54±9.55 years, and 14.96±9.18 years, respectively (p=0.009). The YMRS score of the manic patients was 37.38±7.21 (min: 25, max: 56) and the HAM-D score of depressed patients was 41.74±4.55 (min: 32, max: 51). The characteristics of the groups are provided in Table 1.

In terms of BMI, there was no significant difference between the manic, depressive, and euthymic patients and the healthy controls (27.59±6.58 kg/m^2, 27.56±4.06 kg/m^2, 27.28±5.14 kg/m^2, and 26.03±3.47 kg/m^2, respectively; p=0.503). The manic group was medication-free, with the exception of 3 patients (2 were under treatment with valproate and 1 with lithium). The euthymic patients were under treatment with an antipsychotic (76.2%), lithium (%73.8), valproate (31%), carbamazepine (2.4%), or lamotrigine (2.4%). The depressed patients were medicated with an antipsychotic (94.3%), lithium (62.9%), an antidepressant (37.1%), valproate (28.6%), lamotrigine (17.1%), or carbamazepine (2.9%). Comorbid medical illnesses were present in 2 of the manic patients (1 thyroid disease, 1 hypertension), 9 of the depressive patients (3 thyroid disease, 5 diabetes, 1 hypertension), 3 of euthymic patients (1 thyroid disease, 1 hypertension, 1 diabetes), and 4 of the controls (3 diabetes, 1 thyroid disease) and were under medical treatment. None of participants had a previous history of CVD.

The lipid profile of the manic, depressive, euthymic, and control groups revealed a total cholesterol of 163.77±27.97 mg/dL, 188.88±57.87 mg/dL, 186.54±43.91 mg/dL, and 199.78±38.24 mg/dL, respectively (p<0.001), The low-density lipoprotein cholesterol (LDLc) level was 91.78±27.63 mg/dL, 111.92±60.01 mg/dL, 109.49±39.83 mg/dL, and 127.73±34.70 mg/dL, respectively (p<0.001), while the HDLc level was 43.38±12.38 mg/dL, 38.25±11.04 mg/dL, 44.78±12.52 mg/dL, and 43.97±11 mg/dL in the respective groups (p=0.054). The TG level was 141.15±94.84 mg/dL in the manic group, 217.17±159.68 mg/dL in the depressive group, 160.92±99.96 mg/dL in the euthymic group, and 138.14±66.18 mg/dL in the control group (p=0.014). There was no significant difference between the groups in terms of fasting blood glucose (manic: 96.86±25.26 mg/dL, depressive: 95.28±18.30 mg/dL, euthymic: 99.42±26.18 mg/dL, and control: 96.24±23.69 mg/dL; p=0.673) or glycated hemoglobin (manic: 5.51±0.73%, depressive: 5.64±0.93%, euthymic: 5.39±0.59%, and control: 5.67±1.13%; p=0.452) levels (Table 2).

There was a significant difference in the AIP level between groups (manic: 0.45±0.35, depressive: 0.69±0.34, euthymic: 0.48±0.36, and control: 0.46±0.28; p=0.009). After adjustment for age, BMI, smoking status, and drug medication with ANCOVA, the mean AIP value of the manic, depressive, euthymic, and control groups was 0.46±0.31, 0.60±0.27, 0.51±0.32, and 0.48±0.35, respectively (p=0.014). Statistical significance remained even after adjusting for the effect of confounding factors on AIP. Pairwise comparisons of the groups demonstrated that the AIP level of the depressive patients was significantly higher than seen in the manic, euthymic, and control groups (p=0.013, p=0.048, and p=0.021, respectively) However, there was no significant difference in the comparison of the manic and euthymic, manic and

Table 1. Characteristics of the groups

	Manic	Depressive	Euthymic	Control	*p*
Age (years)	38.22±11.37	41.54±10.29	40.52±10.90	39.02±10.69	0.530
Duration of illness (years)	11.65±9.42	17.54±9.55	14.96±9.18	–	0.009
Young Mania Rating Scale score	37.38±7.21	–	–	–	–
Hamilton Depression Rating Scale score	–	41.74± 4.55	–	–	–
Body mass index (kg/m^2)	27.59±6.58	27.56±4.06	27.28±5.14	26.03±3.47	0.503
Waist circumference (cm)	104.27±17.47	102.88±11.20	98.90±14.99	96.41±11.13	0.041
Metabolic syndrome (yes)	22.7%	37.1%	16.6%	19.5%	0.165
Smoking status (yes)	70.4%	68.5%	50%	63.4%	0.207

control, and euthymic and control groups in terms of AIP (p=0.968, p=0.999, and p=0.988, respectively) (Table 3). When the groups were divided according to AIP risk classification (AIP value of -0.3 to 0.1 is associated with a low risk, 0.1 to 0.24 with a medium risk, and greater than 0.24 with a high cardiovascular risk), 18.2% (n=8) of the manic patients, 16.6% (n=7) of the euthymic patients, and 14.6% (n=7) of the controls were classified as low risk, whereas none of depressive patients were in the low-risk group. All of the depressive patients were in the medium 6% (n=2) or high 94% (n=33) risk groups. The AIP levels and lipid profile parameters are shown in Table 2.

The AIP level was positively correlated with BMI (ro=0.367; p<0.001), waist circumference (ro=0.302; p<0.001), presence of metabolic syndrome (ro=0.511; p<0.001), total cholesterol (ro=0.332; p<0.001), LDLc (ro=0.187; p=0.017), TG (ro=0.872; p<0.001), and negatively correlated with HDLc (ro=-0.810; p<0.001). No correlation was observed between AIP and smoking status (ro=0.187; p=0.017), the total number of previous bipolar episodes (ro=-0.004; p=0.964), previous manic episodes (ro=-0.061; p=0.511), previous depressive episodes (ro=0.023; p=0.832), duration of illness (ro=0.122; p=0.185), or total hospitalization (ro=-0.055; p=0.553).

DISCUSSION

In the current study we aimed to evaluate the effect of BD states on cardiovascular risk. It is an important issue for clinicians to be able to predict the risk factors promoting CVD. Routine biochemical parameters, such as a lipid profile, are easily obtainable and useful laboratory findings to use in the assessment of cardiovascular risk. In the case of a normal lipid profile, if cardiovascular risk cannot be ruled out, certain ratios of lipid parameters may be useful to identify

Table 2. Comparison of the atherogenic index of plasma and lipid profile of the patients and healthy controls

	Manic	Depressive	Euthymic	Control	*p*
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Atherogenic index of plasma[α]	0.45±0.35	0.69±0.34	0.48±0.36	0.46±0.28	0.009
	0.46±0.31[n]	0.60±0.27[n]	0.51±0.32[n]	0.48±0.35[n]	0.014
Total cholesterol (mg/dL)[β]	163.77±27.97	188.88±57.87	186.54±43.91	199.78±38.24	<0.001
Low density lipoprotein (mg/dL)[β]	91.78±27.63	111.92±60.01	109.49±39.83	127.73±34.70	<0.001
High density lipoprotein (mg/dL)[β]	43.38±12.38	38.25±11.04	44.78±12.52	43.97±11	0.054
Triglyceride (mg/dL)[β]	141.15±94.84	217.17±159.68	160.92±99.96	138.14±66.18	<0.014
Fasting blood glycose (mg/dL)[α]	96.86±25.26	95.28±18.30	99.42±26.18	96.24±23.69	0.673
HbA1c[α] (%)	5.51±0.73	5.64±0.93	5.39±0.59	5.67±1.13	0.452

[α]One-way analysis of variance test and β Kruskal Wallis test were used. [n]AIP level adjusted for age, body mass index, smoking status, and drug medication using analysis of covariance. SD: Standard deviation; HbA1c: Glycated hemoglobin.

Table 3. Pairwise comparisons (p values) of the atherogenic index of plasma and the lipid profile

	[α]Atherogenic index of plasma	[β]Total cholesterol	[β]Low density lipoprotein	[β]High density lipoprotein	[β]Triglyceride
Depressive vs. Manic	0.013	0.046	0.232	0.037	0.003
Depressive vs. Euthymic	0.047	0.724	0.404	0.016	0.063
Depressive vs. Control	0.021	0.076	0.003	0.019	0.005
Manic vs. Euthymic	0.967	0.006	0.029	0.647	0.304
Manic vs. Control	0.999	<0.001	<0.001	0.819	0.604
Euthymic vs. Control	0.987	0.155	0.025	0.859	0.597

[α]Tukey's post-hoc analysis and [β]Mann-Whitney U tests were used.

the high-risk group.[4] In our study, when we evaluated the lipid parameters individually, with respect to total cholesterol and LDLc, the control group was at high risk; with respect to TG, the depressive patients were in the high-risk group. Therefore, according to our results, AIP appears to be more useful than the individual lipid parameters to determine the real high-risk group for CVD.

In terms of AIP, as a major finding, our study results indicated that a BD depressive state was associated with cardiovascular risk, rather than manic or euthymic states. In a study conducted by Nunes et al.,[5] 134 patients with a mood disorder (both unipolar depression and bipolar disorder) and 197 controls were evaluated, and atherogenic indices, including AIP, were found to be significantly higher in the patient group. However, the heterogeneous patient group and the lack of details of the BD subtype and episode make it difficult to compare this study with our results. In contrast to our finding, another study evaluating cardiovascular risk in patients with unipolar depression and bipolar depression using the Castelli risk indices demonstrated that unipolar depression but not BD depression was associated with increased atherogenic risk.[6]

Cardiovascular risk in BD patients is complex and multifactorial. Lifestyle factors, such as smoking, poor physical activity and diet, obesity, psychosocial factors such as low occupational status, poor income, and long-term psychotropic medication promote cardiovascular risk.[7]

Although antipsychotic therapy is essential for the treatment of BD, studies have reported metabolic disturbances such as dyslipidemia associated with the use of antipsychotics.[8] Large ratios of increased TG and decreased HDLc levels, resulting in greater metabolic syndrome risk were observed in BD patients receiving antipsychotics.[9] Among mood stabilizers, lithium has been associated with modest weight gain and an increase in TG level.[10] Valproate treatment for BD may also increase the risk of metabolic disturbances. In a study, valproate was found to be associated with dyslipidemia of high TG and low HDLc levels.[11] Pérez-Piñar et al.[12] demonstrated that the use of antidepressants was independently associated with a greater risk for diabetes, hypertension, and hyperlipidemia, and that antipsychotic use was independently associated with a greater risk for diabetes. Although our euthymic group was under medication with antipsychotics and mood stabilizers, interestingly, no significant difference was observed in AIP when compared with the control group. A large percentage of our depressive BD subjects were under treatment with antipsychotics (94.3%), as well as mood stabilizers and antidepressants (37.1%). However, psychotropic medication was also present in both the euthymic and depressed groups. Observing an increased AIP only in the depressed group suggests that additional risk factors may contribute to cardiovascular risk.

Mood disorders are associated with increased atherogenicity. Although the data are inconsistent, depression is associated with reduced HDLc, and increased LDLc, and TG.[13,14] One of the suggested mechanisms of observed associations is that cholesterol plays an integral role in the structure and function of cell membranes in the central nervous system. A high cholesterol level may also influence serotoninergic activity, which is well known to play a role in developing depression.[14] In a study conducted by Bortolasci et al.,[15] both BD and major depressive disorder (MDD) were related to an increased TG level and a lower HDLc. Despite the fact that atherogenicity was found to be a common factor in mood disorders and metabolic syndrome, insulin resistance and BMI were not relevant to mood disorders. Increased oxidative stress, decreased endogenous antioxidants and anti-inflammatory agents, increased atherogenic indices (increased AIP, Castelli indices) were found be useful to delineate MDD/BD patients at risk for comorbid CVD.[16] The hypothalamic-pituitary-adrenal (HPA) axis has an important role in the human stress (physical and emotional) response. HPA axis dysfunction is a characteristic of a subset of approximately one-half of clinically depressed patients. An altered HPA axis function may be another common pathway in comorbid CVD in depression.[17]

Depression is associated with poor physical activity and sedentary behavior. It has been demonstrated that BD patients who had a low physical activity status had a higher risk for cardiometabolic diseases.[18] The depressive state of BD might contribute to the risk of CVD in factors such as increased appetite, excessive intake of carbohydrate-rich foods causing weight gain, cardiac autonomic instability, and increasing blood coagulation.[19] The abovementioned lifestyle is more often observed in a depressive episode than in

the manic and euthymic states, indicating that these lifestyle changes may additionally contribute to cardiovascular risk in depressed patients.

Similar to our finding, earlier literature reports indicated that the manic state had no additional or negative influence on major lipid factors of cardiovascular risk. In a comparison of BD depressive[20,21] and euthymic[22] patients and controls,[23] lower cholesterol levels were observed in the manic patients. In terms of TG and LDLc, manic patients had the lowest values when compared with unipolar depressed patients, BD depressed patients, and controls.[21]

Limitations of the current study include its cross-sectional nature and the relatively small sample size. Although including only the male gender is not representative of the entire BD population, we eliminated the hormonal effect and gender differences on serum lipids, which may be seen as both an advantage and a limitation of our study. Another limitation is that we did not systematically assess insulin resistance parameters, such as the homeostatic model assessment of insulin resistance) or lifestyle factors, such as dietary habits and physical activity of our participants, all of which could affect the cardiovascular risk level.

In conclusion, the results of the current study indicate that the BD depressive state is accompanied by increased AIP, which has a potential to reflect cardiovascular risk. The significant correlations between AIP and other conventional cardiovascular risk factors indicate that AIP may be more useful than absolute lipid parameters to identify BD individuals at high risk for CVD.

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Keywords: Atherogenic index of plasma; bipolar disorder; cardiovascular risk.

Anahtar sözcükler: Aterojenik plazma indeksi; bipolar bozukluk; kardiyovasküler risk.