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Evaluation of Glucagon-like Peptide-1, Adropin, and Desnutrin Levels and Related Factors in Patients with Bipolar Disorder

ABSTRACT

Objective: It is known that impaired energy metabolism contributes to the neuropathology of bipolar disorder (BD). This study aimed to compare the levels of glucagon-like peptide-1 (GLP-1), adropin, and desnutrin, which have many metabolic functions besides the regulation of energy metabolism, between patients with BD and healthy controls and to investigate the related factors.

Methods: In the study group, 73 age- and sex-matched participants were included. Of them, 35 were patients diagnosed with BD and 38 were healthy individuals. In the blood samples, in addition to routine biochemistry lipid parameters, the levels of adropin, desnutrin, and GLP-1 were determined.

Results: Adropin, desnutrin, and GLP-1 levels were significantly lower in patients with BD than in healthy controls ($P < 0.001$). In contrast, body mass index, total cholesterol, triglyceride, and low-density lipoprotein levels were significantly higher in patients with BD than in healthy controls (respectively $P < 0.001$, $P = 0.001$, $P = 0.002$, $P = 0.001$). It was observed that adropin levels decreased significantly as the duration of the disease increased.

Conclusion: The low levels of adropin, desnutrin, and GLP-1 that we determined in patients with BD indicate that these peptides may be important in BD pathophysiology.

Keywords: Bipolar disorder, adropin, desnutrin, glucagon-like peptide-1

Introduction

Bipolar disorder (BD) is a recurrent disorder with manic and depressive episodes and seizures, and it may become chronic from time to time. If it is not followed up and treated regularly, the patients' social and occupational functionality may be impaired, and their quality of life may decrease.[1] BD affects 1-3% of the population worldwide.[2] Although increasing evidence has focused on the epidemiology, symptoms, and complications of BD, its etiology and pathophysiology have not been adequately clarified.[3] In addition to mood symptoms, patients diagnosed with BD are at a risk of both psychiatric and medical comorbidity.[4] Several factors can lead to this. Especially during both depressive and mixed seizures of BD, patients may experience decreased mobility, increased appetite, and malnutrition. In addition, increased appetite and weight gain, which are among the side effects of mood stabilizers and atypical antipsychotic and antidepressant medications used in the treatment of BD, are common.[2] Impaired energy metabolism is known to contribute to the neuropathology of BD.[5]

Adropin, desnutrin, and glucagon-like peptide-1 (GLP-1) are among the peptides involved in energy metabolism and several metabolic functions.[6-8] Adropin is a protein encoded by the energy homeostasis-associated gene expressed primarily in the liver and brain.[9]

In recent years, the role of adropin in the central nervous system (CNS) has also been studied. Adropin, a membrane-bound protein in the CNS, has been shown to regulate physical activity and motor coordination and plays an important role in the development of the cerebel-

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lum in mice.[10] However, it has been reported that it reduces oxidative damage and thus has a neuroprotective effect.[11]

Desnutrin (adipose triglyceride lipase) is a member of a family of proteins (nutrines), which plays a role in the regulation of lipolysis in adipose tissue in response to nutritional conditions.[12] Expression of desnutrin is increased by glucagon and glucocorticoids during fasting and decreased by insulin during satiety.[7]

Data on the role of desnutrin in the CNS are limited. In a study conducted with genetically modified mice, desnutrin deficiency was found to cause an increase in triacylglycerol (TAG) fractions in the brain. Therefore, desnutrin is thought to be necessary for providing the fatty acids that the brain needs. It is also claimed that desnutrin may be involved in an additional mechanism of cerebral lipid control.[13]

GLP-1 is a peptide hormone belonging to the family of incretins, which has important effects on glucose homeostasis, and it is secreted by the L cells in the small intestine in response to food intake. GLP-1 stimulates insulin secretion in response to glucose after food intake and inhibits the secretion of glucagon.[8] Owing to its appetite-reducing effect, GLP-1-derived drugs have been used in the treatment of obesity.[14]

In recent years, although considerable research has been devoted to the investigation of the regulators of lipid and glucose metabolism in patients with BD, the number of studies investigating adropin, desnutrin, and GLP-1 levels in BD is very few. It has been reported that adropin can be used as a therapeutic agent in neuropsychiatric diseases, such as Parkinson's disease and schizophrenia.[15, 16] Most of these studies have focused on GLP-1. It has been reported that studies have been conducted on GLP-1 in patients with schizophrenia, Alzheimer's disease, BD, and other neurodegenerative diseases.[8, 17-21]

This study aimed to compare patients with BD with healthy controls in terms of adropin, desnutrin, and GLP-1 levels, which regulate the energy metabolism and have many metabolic functions, and to investigate the related factors. Our research hypothesis is as follows: there is a difference between patients diagnosed with BD and healthy controls in terms of adropin, desnutrin, and GLP-1 levels. We believe that our study data will bridge the gap in this area in the literature and that energy metabolism can play an important role in the pathophysiology of BD.

Methods

The study included 35 patients with BD aged between 20 and 57 years who were followed-up and treated at the Niğde Ömer Halisdemir University Training and Research Hospital, Psychiatry Outpatient Treatment Unit, and randomly selected within a 1-month period and 38 healthy controls in the same age group. The participants in the patient and healthy control groups signed the informed consent forms. The ethics committee of the Niğde Ömer Halisdemir University approved this study (Approval Date: June 1, 2020; Approval Number: 2020/05-23). All practices in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards.

MAIN POINTS

- *Impaired energy metabolism contributes to the neuropathology of bipolar disorder (BD).*
- *The regulatory effect of adropine on the fat and carbohydrate metabolism is impaired in BD patients.*
- *Low levels of adropine, desnutrin, and glucagon-like peptide-1 may be important in the pathophysiology of BD.*

The diagnosis of BD was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Of the patients with BD, those who agreed to participate in the study were included in the patient group. Those with neurodegenerative diseases, comorbid psychiatric disorders (schizoaffective disorder), systemic disease (cardiovascular diseases, endocrine system diseases, and so on), alcohol or substance addiction, Alzheimer's disease, or Parkinson's disease were excluded. Volunteers without any psychiatric, neurological, and systemic diseases and alcohol or substance addiction were included in the control group. Evaluation of the medical status of the participants in the patient and control groups was performed on the basis of their medical documents and self-reports.

Data Collection Tools

Sociodemographic and Clinical Characteristics Form: The form included items questioning all the participants' sociodemographic characteristics, such as age, gender, height, and weight, and the clinical characteristics of the participants in the patient group, such as the stage of the disease, duration of the disease, and the drugs they took. Body mass index (BMI) of the participants in the patient and control groups was calculated.

Laboratory Procedures

From each participant in the patient and control groups, 6 mL of venous blood samples were taken into 2 empty tubes containing sterile gels after 12 hours of fasting. Measurements of routine biochemistry lipid parameters in the serum sample (Tube 1) were performed in the autoanalyzer. The other serum sample (Tube 2) was stored at -80°C until the day when the levels of adropin (SinoGeneClon- Cat. No: 11594), desnutrin (SinoGeneClon-Cat. No: 10503), and GLP-1 (SinoGeneClon- Cat. No: 10241) were measured. The adropin, desnutrin, and GLP-1 levels in the serum samples were determined in accordance with the enzyme-linked immunosorbent assay (ELISA) kit protocol using the ELISA reader (Model: GF-M3000, Caihong Co. Ltd.; Xianyang, China).

Statistical Analysis

The data obtained from our study were analyzed in the IBM Statistical Package for the Social Sciences (version 20) program (IBM Corp.; Armonk, NY, USA). The Kolmogorov-Smirnov test was used to find out whether the variables were distributed normally. It was observed that the groups were normally distributed. Because the parametric test assumptions were fulfilled, the independent samples *t*-test was used to compare the differences between the 2 groups. One-way analysis of variance and the Tukey test were used to compare more than 2 groups, and the Pearson's chi-square test was used to compare the categorical data. Variables were analyzed at 95% confidence level, and $P < 0.05$ was considered statistically significant.

Results

The study included 73 people. Of them, 35 were patients with BD and 38 were healthy controls.

There was no statistically significant difference between the patient and the control groups in terms of gender distribution ($P = 0.729$) (Table 1).

The data on the participants' age, BMI, and adropin, desnutrin, GLP-1, and serum lipid parameter levels (total cholesterol [TChol], triglyceride [TG], high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) are given in Table 2.

There was no statistically significant difference between the two groups in terms of age. The mean BMI value was significantly higher in the patient group (29.35 [SD = 3.78]) than in the control group (26.82 [SD = 1.91]) ($P < 0.001$). Adropin, desnutrin, and GLP-1 levels were 88.15 (SD = 31.40) ng/mL, 8.01 (SD = 1.46) ng/mL, and 51.94 (SD = 13.00) ng/mL, respectively, in the patient group and 125.52 (SD = 19.75) ng/mL, 12.02 (SD = 1.75) ng/mL, and 115.94 (SD = 49.20) ng/mL, respectively, in the control group. Adropin, desnutrin, and GLP-1 levels were significantly lower in the patient group than in the control group ($P = 0.001$). The TChol level was 204 (SD = 65.31) mg/dL in the patient group and 115 (SD = 32.03) mg/dL in the control group. The TG level was 163.18 (SD = 32.38) mg/dL in the patient group and 125 (SD = 51.02) mg/dL in the control group. The LDL level was 180 (SD = 116.95) mg/dL in the patient group and 93.95 (SD = 25.79) mg/dL in the control group. The differences between the patient and control groups in terms of TChol, TG, and LDL levels were statistically significant (respectively $P = 0.001$, $P = 0.002$, $P = 0.001$). The HDL level was 49.06 (SD = 13.98) mg/dL in the patient group and 49.00 (SD = 8.79) mg/dL in the control group, and the difference between the groups was not statistically significant ($P = 0.983$).

In the patient group, the comparison of the stage and duration of the disease in terms of adropin, desnutrin, and GLP-1 levels is shown in Table 3. There was no significant relationship between the disease stages and adropin, desnutrin, and GLP-1 levels (respectively $P = 0.705$, $P = 0.459$, $P = 0.466$). Although there was no significant relationship between the duration of the disease and the levels of desnutrin and GLP-1 (respectively $P = 0.675$, $P = 0.318$), there was a significant relationship between the duration of the disease and adropin levels ($P < 0.001$). It was observed that adropin levels decreased as the duration of the disease increased.

Table 1. Distribution of the Participants in the Patient and Control Groups by Gender

	Patient group	Control group		
Gender	n (%)	n (%)	χ^2	*P*
Female	17 (48.6)	20 (52.6)		
Male	18 (51.4)	18 (47.4)	0.12	0.729
Total	35 (100)	38 (100)		

Table 2. Data on the Age, BMI, and Adropin, Desnutrin, GLP-1, and Serum Lipid Parameter Levels of the Participants in the Patient and Control Groups

	Patient group	Control group	t	*P*
Age, mean (SD), year	40.14 (11.12)	40.26 (11.22)	-0.046	0.963
BMI, mean (SD), kg/m^2	29.35 (3.78)	26.82 (1.91)	3.648	< 0.001[a]
ADP, mean (SD), ng/mL	88.15 (31.40)	125.52 (19.75)	-6.138	< 0.001[a]
DES, mean (SD), ng/mL	8.01 (1.46)	12.02 (1.75)	-10.566	< 0.001[a]
GLP-1, mean (SD), ng/mL	51.94 (13.00)	115.94 (49.20)	-7.456	< 0.001[a]
FBS, mean (SD), mg/dL	92.91 (16.22)	90.08 (10.69)	0.889	0.377
Cholesterol, mean (SD), mg/dL	204.86 (65.31)	163.18 (32.38)	3.496	0.001[a]
TG, mean (SD), mg/dL	180.34 (116.95)	11.37 (32.03)	3.295	0.002[b]
HDL, mean (SD), mg/dL	49.06 (13.98)	49.00 (8.79)	0.021	0.983
LDL, mean (SD), mg/dL	125.86 (51.02)	93.95 (25.79)	3.412	0.001[a]

Abbreviations: BMI, body mass index; ADP, adropin; DES, desnutrin; GLP-1, glucagon-like peptide-1; FBG, fasting blood glucose; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]$P \leq 0.001$.
[b]$P \leq 0.05$.

Table 3. Comparison of the Stage and Duration of the Disease in Terms of Adropin, Desnutrin, and GLP-1 Levels in Participants in the Patient Group

			Adropin		Desnutrin		GLP-1	
		n (%)	Mean (SD)	*P*	Mean (SD)	*P*	Mean (SD)	*P*
Stage	Euthymic	21 (60)	91.04 (35.04)	0.705	7.87 (1.75)	0.459	54.10 (13.24)	0.466
	Depressive	7 (20)	79.30 (28.63)		8.63 (1.02)		47.40 (12.92)	
	Manic	7 (20)	88.33 (23.58)		7.80 (0.56)		50.02 (12.72)	
Period	0-5 years	12 (34.2)	123.64 (19.12)	< 0.001[a]	8.16 (1.27)	0.675	47.39 (9.82)	0.318
	6-10 years	7 (20)	87.95 (16.39)		8.17 (0.42)		58.63 (14.31)	
	11-15 years	8 (22.9)	62.75 (11.64)		7.43 (2.46)		50.81 (13.39)	
	≥16 years	8 (22.9)	60.48 (8.88)		8.20 (1.08)		54.04 (15.08)	

Abbreviations: GLP-1, glucagon-like peptide-1; SD, standard deviation.
[a]$P \leq 0.001$.

Table 4. Pearson's Correlation Analysis between BMI and Adropin, Desnutrin, GLP-1, and Lipid Parameter Levels of the Participants in the Patient Group

		BMI	ADP	DES	GLP-1	TChol	TG	HDL	LDL
BMI	Pearson	1	0.071	-0.047	-0.015	0.244	-0.066	-0.010	0.327
	P		0.685	0.788	0.931	0.157	0.707	0.955	0.055
ADP	Pearson	0.071	1	0.070	-0.088	0.112	0.146	-0.118	0.089
	P	0.685		0.688	0.616	0.521	0.402	0.499	0.610
DES	Pearson	-0.047	0.070	1	-0.160	0.212	0.267	0.071	0.287
	P	0.788	0.688		0.359	0.222	0.121	0.683	0.095
GLP-1	Pearson	-0.015	-0.088	-0.160	1	-0.106	0.191	-0.267	0.030
	P	0.931	0.616	0.359		0.545	0.272	0.121	0.866
TChol	Pearson	0.244	0.112	0.212	-0.106	1	0.435	0.502	0.914
	P	0.157	0.521	0.222	0.545		0.009[a]	0.002[a]	< 0.001[b]
TG	Pearson	-0.066	0.146	0.267	0.191	0.435	1	-0.175	0.442
	P	0.707	0.402	0.121	0.272	0.009[a]		0.313	0.008[a]
HDL	Pearson	-0.010	-0.118	0.071	-0.267	0.502	-0.175	1	0325
	P	0.955	0.499	0.683	0.121	0.002[a]	0.313		0.057
LDL	Pearson	0.327	0.089	0.287	0.030	0.914	0.442	0.325	1
	P	0.055	0.610	0.095	0.866	< 0.001[b]	0.008[a]	0.057	

Abbreviations: BMI, body mass index; ADP, adropin; DES, desnutrin; GLP-1, glucagon-like peptide-1; TCHOL, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]$P \leq 0.05$.
[b]$P \leq 0.001$.

Correlation between age; BMI; serum adropin, desnutrin, and GLP-1 levels; and lipid parameters (TChol, TG, HDL, and LDL) of the participants in the patient group is shown in Table 4. As is seen in the table, there was a significant positive relationship only in the lipid parameters (TChol- TG $P = 0.009$, Chol- HDL $P = 0.002$, TChol- LDL $P < 0.001$, TG-LDL $P = 0.008$).

Discussion

In this study, we compared the adropin, desnutrin, and GLP-1 levels of patients with BD with those of healthy controls.

At the end of the study, the serum adropin, desnutrin, and GLP-1 levels of patients with BD were significantly lower than those of the healthy controls ($P < 0.001$).

In many studies, adropin has been shown to be associated with diabetes mellitus (DM),[22] coronary artery disease,[23] and obesity.[24] In these studies, as in our study, adropin levels were found to be low.

In many studies, adropin has been reported to be associated with cellular signaling pathways.[25] Adropin promotes the proliferation of preadipocytes through these signaling pathways,[26] which may reduce dyslipidemia and associated pathologies through the formation of small-sized adipocytes.[27] These signaling pathways influenced by adropin are known to play an important role in the pathophysiology of BD.[28] The data obtained in our study indicate that the regulatory effect of adropin on fat and carbohydrate metabolism is impaired in patients with BD.

It has also been suggested that adropin could be used as a therapeutic agent in neuropsychiatric diseases, such as Parkinson's disease and schizophrenia, by activating these signaling pathways.[15, 16]

The number of studies investigating desnutrin levels in diseases is few.[29] Experimentally, genetically modified mice with desnutrin deficiency were created. In a study conducted with such mice, it has been reported that TAG storage in adipose tissues increased significantly and caused fatal cardiac TAG accumulation in the cardiomyocytes of mice.[30] Desnutrin levels have been reported to be low in DM and obesity.[31] The decrease in the level of desnutrin leads to a decline in fatty acids that the brain needs and the accumulation of TAG, which may impair brain-lipid homeostasis. As in many diseases, it can be assumed that such effects are likely to occur in BD. However, low desnutrin levels detected in BD indicate that the risk of comorbid diseases, such as metabolic syndrome, DM, and obesity, is high.

Almost all studies conducted with patients diagnosed with BD are on the GLP-1 levels.[18-21] In studies conducted on Alzheimer's and other neurodegenerative diseases, GLP-1 has been reported to have a protective effect in these diseases.[8]

Ando et al[17] have reported that GLP-1 receptor agonists are effective in patients with diabetic schizophrenia treated with second-generation antipsychotics. Olanzapine, a second-generation antipsychotic, which is known to be associated with weight gain, has been shown to cause significant increases in postprandial insulin, GLP-1, and glucagon levels compared with placebo.[19]

Rosso et al[20] have found that GLP-1 levels were lower in patients with BD than in healthy controls. No correlation was determined between GLP-1 levels and the severity of symptomatology, disease subtypes, and treatment of patients with different drugs. In our study, serum GLP-1 levels of the patients with BD were found to be significantly lower than those of the healthy controls, which was consistent with the results of the study by Rosso et al.[20] The lack of neurotrophic support owing to dysregulation of GLP-1 might be one of the shared mechanisms between metabolic alterations and BD.[14, 21]

BMI values in the patient group were higher than those in the control group ($P < 0.001$). Of the lipid parameters, TChol, TG, and LDL values were also significantly higher in the patient group than in the control

group (respectively $P = 0.001$, $P = 0.002$, $P = 0.001$). This is a precursor of cardiac problems, insulin resistance, obesity, and comorbidities associated with increased depot TAG and decreased lipolysis. In many studies conducted with patients with BD, BMI values were determined to be higher than those in healthy controls.[32, 33]

In our study, no correlation was found between disease stages and adropin, desnutrin, and GLP-1 levels. Similarly, in the study conducted by Rosso et al[20] with 57 patients with BD and 49 healthy individuals, no correlation was determined between GLP-1 levels and the subtypes of the disease.[20]

In this study, it was observed that the level of adropin decreased significantly as the duration of the disease increased. In many studies, it has been determined that the brain-derived neurotrophic factor (BDNF) is a biochemical marker in BD and that peripheral blood levels BDNF of patients with BD are lower than those of healthy controls.[34] Adropin activates cellular signaling and thus causes the expression of molecules, such as BDNF.[35] In diseases, such as schizophrenia and BD, as the duration of the disease increases, BDNF levels decrease.[36, 37] In this study, as the disease duration increased, adropin levels decreased, which may be related to the decrease in BDNF levels. The decrease in adropin levels resulting from the increase in the disease duration suggests that adropin has an effect on the pathogenesis of BD.

In the patient group, although the stage and duration of the disease were evaluated, clinical factors, such as the number of mood periods, number of hospitalizations, the severity of the disease, and compliance with treatment, were not evaluated.

In the patient group, the relationship between age; BMI; serum adropin, desnutrin, and GLP-1 levels; and lipid parameters were evaluated. However, a positive relationship was detected only between lipid parameters, such as TChol, TG, HDL, and LDL. These data are an expected result owing to the relationship between these molecules. There was no significant relationship between BMI and the parameters investigated. Therefore, we can say that BMI levels have no effect on adropin, desnutrin, and GLP-1 levels.

Our study is the first in the literature in which adropin, desnutrin, and GLP-1 levels in patients diagnosed with BD were evaluated together, which makes our study valuable. However, this study has several limitations. First, the patient group consisted of patients diagnosed with BD who were taking medication. The medication that the patients took was determined, but no comparison was made according to the medication they took. Another limitation of the study is the small number of participants both in the patient and control groups. Characteristics of the participants, such as diet, lifestyle, and smoking status, were not also evaluated.

In conclusion, studies have indicated the importance of the regulation of energy metabolism in many diseases. Our findings point to the metabolic effects of adropin, desnutrin, and GLP-1 in BD by measuring their levels and broaden the information about these peptides. The low levels of adropin, desnutrin, and GLP-1 that we identified in patients with BD suggest that these peptides may be important in the pathophysiology of BD. However, extensive studies should be conducted to confirm our data. We expect that such studies will eliminate the deficiency in this area.

Ethics Committee Approval: *Ethics committee approval was received for this study from the Ethics Committee of Niğde Ömer Halisdemir University (Approval Date: June 1, 2020; Approval Number: 2020/05-23).*

Informed Consent: *Informed consent was obtained from the patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

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