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GHRELIN AND LIPID LEVELS IN PANIC DISORDER BEFORE AND AFTER TREATMENT AND THEIR RELATIONSHIP WITH AGORAPHOBIA

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SUMMARY

Background: *We aimed to evaluate serum ghrelin (GHR) levels and lipid profile in panic disorder (PD), with and without agoraphobia, and to compare these parameters before and after treatment.*

Subjects and methods: *The GHR and lipid profiles were measured in blood samples taken from 31 PD patients with agoraphobia, 22 PD patients without agoraphobia, and 53 control group subjects. 23 of the 53 patients who were prescribed 20 to 40 mg/day paroxetine had continued treatment. The 23 patients who had continued treatment were measured again at the end of twelve weeks.*

Results: *The GHR and triglyceride (TRG), total cholesterol (Total-C), low-density lipoproteins (LDL-C), and very low-density lipoproteins (VLDL-C) levels were higher in the PD with agoraphobia group than the PD without agoraphobia and control groups. The 23 patients that had continued their treatment were re-evaluated, and the serum GHR, Total-C levels, and BMI after treatment were significantly decreased, compared to the values before treatment.*

Conclusions: *There may be a pathophysiological relationship between the GHR and lipid profiles that interact with each other in PD. In fact, this relationship was more marked in PD with agoraphobia than in PD without agoraphobia.*

Key words: *panic disorder – agoraphobia – ghrelin – lipid - cholesterol*

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INTRODUCTION

Panic disorder (PD) is a chronic anxiety disorder characterized by unexpected panic attacks, which decrease occupational and social functioning. Panic attacks last about 15-20 minutes, with symptoms such as palpitation, shortness of breath, chest pain, fear of death, and fear of losing control. The person suffering from PD avoids crowds, being alone outside the home, and activities such as traveling, where it is difficult to run away or get help due to the fear of new seizures (anticipatory anxiety) and suffers intense anxiety in these situations, known as "agoraphobia" (Grillon 2005, Bayraktar 2008). Epidemiological field studies report that agoraphobia accompanies 30% to 50% of all PD cases (Bayraktar 2008). Although many studies tried to explain the aetiology of PD, the subtypes of PD, with and without agoraphobia, the current hypotheses are not clear to explain the aetiology of PD (Crowe et al. 1983, Marks 1986, Nutt 1989, Papp et al. 1993, Bell & Nutt 1998, Vythilingam et al. 2000, Sakai et al. 2005).

Ghrelin (GHR) and lipid profiles have been recently explored as explanations for the pathophysiology of psychiatric disorders in recent years. GHR is a 28-amino acid hormone, discovered for the first time in 1999 by Kojima et al. (1999) as a hormone ligand of the growth hormone-releasing receptor. GHR is produced in many places, such as the kidney, placenta, pituitary gland, the hypothalamus, and especially the gastrointestinal tract, and serves as a physiological mediator for the feedback signals between gastric functions and the central nervous system in the regulation of food intake (Kojima & Kangawa 2005). The appetite and fat tissue increasing effects of GHR are thought to be independent of growth hormone increasing effects and regulated by special neurons in the central nervous system through leptin. GHR levels decrease with obesity and calorie intake and increase with hunger and in anorexia nervosa (Casanueva & Dieguez 2002). Recent studies report that the appetite-stimulating effect of GHR may be regulated by serotonin and the suppression of hypothalamic dopamine release. Binge eating and vomiting behaviours in eating disorders are associated with increased GHR concentrations (Brunetti et al. 2002), and the variability in leptin levels disappears and GHR levels increase in major depression (Kalra et al. 1999, Brunetti et al. 2002, Tanaka et al 2004).

It is reported that GHR's effects on appetite and body fat ratio is regulated by the special neurons in the central nervous system where leptin is a mediator. Leptin increases energy consumption, and reduces appetite. And GHR antagonizes this anorexigenic effect of leptin via hypothalamic neuropeptide Y/Y1 receptor. Therefore, there is a metabolic antagonism between GHR and leptin (Shintani et al. 2001, Schellekens et al. 2012). Leptin affected intracellular lipid concentration by

decreasing fatty acid and TRG levels and increasing lipid oxidation. Additionally leptin had a positive correlation with Total-C, LDL-C, TRG and body fat ratio (Emül et al. 2007). It is known that there is a relationship between high blood lipids and certain psychiatric disorders. In studies evaluating blood lipid levels of patients with PD, high Total-C and TRG levels has been reported (Agargün et. al. 1996, Yamada et. al. 1997). Lipid concentration changes in neurons breaks the transmission function at receptor level (Davidson et al. 1996, Yamada et. al. 1997). In a study, patients with obsessive compulsive disorder (OCD) and patients with comorbidity of OCD and major depression (MD) were compared in terms of serum GHR, leptin and lipid levels. In the group of OCD+MD, high serum GHR and low serum leptin levels were found. In this study, negative correlation between GHR and leptin levels was found in the group with OCD+MD comorbidity, however, any relationship between serum GHR- and leptin-levels and lipid profile was not found (Emül et al. 2007). In a study on patients with bipolar disorder, a positive correlation between leptin levels and Total-C was found (Atmaca et al. 2002).

Several studies suggest that GHR mediates some of the usual behavioural responses to acute and chronic stress; circulating GHR levels rise after stress. Thus, it seems likely that certain circulating hormones and critical neuroanatomical circuits exist that regulate both energy homeostasis and our psychological state. The peptide hormone GHR is one such mediator, linked to food intake and body weight behaviours and behaviours associated with psychosocial stress, mood, and anxiety (Richardson et al. 2003, Vieweg et al. 2006).

To our knowledge, the relation between GHR and PD with and without agoraphobia is unexplored. Therefore, we examined whether serum GHR and lipid levels are associated with the etiopathogenesis of PD, with and without agoraphobia. We hypothesized that GHR levels and lipid profiles in PD with agoraphobia are increased, compared to PD without agoraphobia and healthy controls. Thus, we evaluated serum GHR levels and lipid profiles in patients with PD, with and without agoraphobia, and healthy controls. We also observed how treatment in PD with or without agoraphobia influenced serum GHR and lipids.

SUBJECTS AND METHODS

Subjects and instruments

This study was conducted with 53 patients who presented at the Inonu University Medical Faculty, Turgut Ozal Medical Center's Clinic of Psychiatry, and were diagnosed with PD (31 PD with agoraphobia, 22 PD without agoraphobia) according to the DSM-IV-TR diagnostic criteria, and 53 healthy control group subjects; groups were matched for age and sex. The participants were informed about the procedures to be performed and their written consent was obtained. The research project was approved by the Inönü University Medical Faculty Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. The diagnoses of the patients who participated in the study were determined by a psychiatrist, using a structured interview form (Structured Clinical Interview for the DSM-IV-TR, SCID) prepared according to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders) criteria. Exclusion criteria were as follows: the presence of educational and language problems that would prevent the interview for diagnostic purposes; a diagnosis of comorbid psychiatric disorders; endocrine disorders (such as hypo/hyperthyroidism, adrenal insufficiency, Cushing, diabetes); severe hematopoietic, cardiovascular, or respiratory system diseases; epilepsy, dementia, and neurological disorders; obesity, alcohol, smoking, substance abuse, or presence of addiction; taking any anti-lipidemic drugs that affect blood lipid profile; and another medical treatment in the last 2 months. A personal or family history of any of the exclusion criteria was used as exclusion criteria for the healthy control group. Blood samples were taken from the patient and control groups, in accordance with established procedure, to study GHR, triglyceride (TRG), total cholesterol (Total-C), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and very low-density lipoprotein (VLDL-C) levels. Height (meter) and weight (kilogram) were noted and body mass index (BMI) was calculated as kg/m^2. The Socio-demographic Data Form, Panic and Agoraphobia Scale (PAS), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) were used to collect data. 23 of the 53 patients who were evaluated in outpatient and put on treatment with 20 to 40 mg/day paroxetine, a selective serotonin reuptake inhibitor (SSRI), continued their treatment. The remaining 30 patients were excluded from the study because they did not come regularly to their outpatient follow-up. 23 patients were re-evaluated at the end of 12 weeks using the data collection tools and their BMIs were calculated. Furthermore, blood was drawn again from these patients to study the GHR and lipid profile; blood was stored in accordance with established procedure until the day of analysis at the laboratory.

Procedures

8-10 ml of blood was drawn into a gel biochemistry tube between 08:00 and 09:00 in the morning, after at least 12 hours of fasting, from the 53 patients and 53 healthy control group subjects at the beginning of the study, and again 12 weeks later from the 23 patients that continued the treatment. Blood samples were centrifuged at 4000 rpm for 10 minutes and the serum was separated. The separated sera were transferred into dry sterile tubes and stored at -80°C until laboratory analysis.

Biochemical Analysis

Serum TRG, Total-C, LDL-C, HDL-C, and VLDL-C levels were measured on an Abbott Architect c16000 autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA) using Abbott brand commercial kits.

Serum GHR (human acylated ghrelin) levels were analysed in a BRIO brand ELISA device (Radim spa, Pomezia, Italy) using the Cayman brand commercial EIA kit (Cayman Chemical Company, Ann Arbor, Michigan USA).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 16.0 software was used to analyse study data. Quantitative variables were expressed as mean ± standard deviation (SD), while qualitative variables were expressed as numbers and percentages. A normal distribution was found for quantitative variables with the Shapiro-Wilk normality test (p>0.05). Unpaired T-test, Pearson chi-square analysis, and Fisher's Exact Chi-Square tests were used to compare the patient and control groups. The groups were compared with the paired T-test before and after the treatment. The Wilcoxon Signed-Rank Test was used to compare PD without agoraphobia group before and after treatment. The one-way analysis of variance (ANOVA) test and the two-way ANOVA with the Bonferroni method were used for the three-way comparison of PD with agoraphobia, PD without agoraphobia, and control groups for the GHR, TRG, Total-C, LDL-C, and VLDL-C parameters. The intragroup variables were tested with the Pearson Correlation Analysis. A p value <0.05 was accepted as statistically significant.

RESULTS

The number of subjects and mean age for the PD with agoraphobia group was 31 and 36.9±11.2 years, while the relative numbers for the PD without agoraphobia group were 22 and 36.7±10.5 years. The control group consisted of 53 healthy individuals, 21 (39.6%) males and 32 (60.4%) females. The mean age of the controls was 36.96±10.82 years. There was no significant difference between the PD with agoraphobia group, the PD without agoraphobia group, and control group in terms of age, gender, marital status, or educational level (p>0.05). In the PD group with agoraphobia, the duration of illness was 2.90±1.25 years, and in the PD group without agoraphobia, it was 2.64±1.36 years. Both groups did not differ significantly in terms of duration of illness (p=0.64) (Table 1).

When the PD groups with and without agoraphobia and control group were compared in terms of serum GHR, TRG, total-C, LDL-C, HDL-C, VLDL-C levels and BMI, serum GHR and TRG, total-C, LDL-C, and VLDL-C levels were significantly different (p=0.0001, p=0.0001, p=0.0001, p=0.0001, and p=0.0001, respectively) while there was no statistically significant difference in HDL-C levels or BMI (p=0.77 and p=0.10, respectively). When two-way comparisons of the groups were made to determine the group creating the difference, the serum GHR, TRG, Total-C, LDL-C, and VLDL-C levels in the PD with agoraphobia group were significantly higher than the PD without agoraphobia group (p=0.0001, p=0.0001, p=0.002, p=0.002, and p=0.03, respectively). There was no statistically significant difference in BMI or HDL-C levels between the two groups (p=0.78 and p=0.08, respectively). When the PD with agoraphobia and the control groups were compared, the serum GHR, TRG, Total-C, LDL-C, and VLDL-C levels in the PD with agoraphobia group were statistically significantly higher than in the control group (p=0.0001, p=0.0001, p=0.0001, p=0.0001, and p=0.0001, respectively), while there was no significant difference between the two groups in BMI or HDL-C levels (p=0.85 and p=0.50, respectively). When the PD without agoraphobia group was compared to the control

Table 1. The comparison of PD groups with and without agoraphobia and control group in terms of socio-demographic data

	PD with Agoraphobia (n=31)	PD without Agoraphobia (n=22)	Control (n=53)	p
Age (year) (Mean±SD)	36.9±11.2	36.7±10.5	36.96±10.82	0.99
The duration of the illness (year) (Mean±SD)	2.90±1.25	2.64±1.36		0.64
Gender (n, %)				
Female	19 (61.3%)	13 (59.1%)	32 (60.4%)	0.99
Male	12 (38.7%)	9 (40.9%)	21 (39.6%)	
Marital Status (n, %)				
Married	25 (80.6%)	16 (72.7%)	34 (64.2%)	0.27
Single	6 (19.4%)	6 (27.3%)	19 (35.8%)	
Educational Level (n, %)				
Primary School	11(35.5%)	8 (36.4%)	22 (41.5%)	0.83
High school and above	20 (64.5%)	14 (63.6%)	31 (58.5%)	
Occupation				
Employed	14 (45.2%)	9 (40.9%)	32 (60.4%)	0.18
Not employed	17 (54.8%)	13 (59.1%)	21 (39.6%)	

*: Statistically significant

Table 2. The comparison of the pre-treatment PD with agoraphobia group, PD without agoraphobia group, and the control group regarding serum GHR levels and lipid profile (TRG, Total-C, LDL-C, HDL-C, and VLDL-C)

	PD with agoraphobia (n=31) (mean±SD)	PD without agoraphobia (n=22) (mean±SD)	Control (n=53) (mean±SD)	p
GHR (pg/mL)	9.39±4.24	4.25±1.55	3.03±2.25	*0.0001*a* *0.0001*b* *0.0001*c* 0.22d
TRG (mg/dl)	180.68±74.14	86.41±30.15	103.47±40.27	*0.0001*a* *0.0001*b* *0.0001*c* 0.39d
Total-C (mg/dl)	202.94±43.65	168.77±28.93	153.30±32.75	*0.0001*a* *0.002*b* *0.0001*c* 0.20d
LDL-C (mg/dl)	126.00±34.00	100.77±19.80	96.68±22.77	*0.0001*a* *0.002*b* *0.0001*c* 0.81d
HDL-C (mg/dl)	45.19±6.74	40.45±6.87	43.19±8.87	0.10a 0.08b 0.50c 0.36d
VLDL-C (mg/dl)	32.19±18.95	23.20±10.31	19.13±8.94	*0.0001*a* *0.03*b* *0.0001*c* 0.43d
BMI (kg/m^2)	27.80±2.82	27.20±3.69	27.42±3.09	0.77a 0.78b 0.85c 0.96d

*: Statistically significant, a: Between PD with agoraphobia, PD without agoraphobia and control groups, b: Between the PD with agoraphobia, PD without agoraphobia groups c: Between the PD with agoraphobia and control groups d: Between the PD without agoraphobia and control groups

group, no statistically significant difference was found between the two groups in serum GHR, TRG, Total-C, LDL-C, VLDL-C, HDL-C levels or BMI (p=0.22, p=0.39, p=0.20, p=0.81, p=0.43, p=0.36, and p=0.96, respectively) (Table 2).

When the pre-treatment and post-treatment PD groups were compared in terms of the serum GHR, lipid profile (TRG, Total-C, LDL-C, and HDL-C), and BMI, the serum GHR, Total-C, and BMI levels were statistically significantly lower in the post-treatment PD group than the pre-treatment PD group (p=0.0001, p=0.0001, and p=0.003, respectively). There was no statistically significant difference between the two groups in terms of TRG, LDL-C, HDL-C, or VLDL-C levels (p=0.73, p=0.37, p=0.62, and p=0.20, respectively) (Table 3).

When the pre- and post-treatment PD with agoraphobia groups were compared in terms of the same parameters, the serum GHR, Total-C, and BMI levels in the post-treatment PD with agoraphobia group was significantly lower than in the pre-treatment group (p=0.0001, p=0.0001, and p=0.02, respectively). There was no statistically significant difference between the two groups in terms of TRG, LDL-C, HDL-C, or VLDL-C levels (p=0.28, p=0.27, p=0.22, and p=0.08, respectively) (Table 4).

Table 3. The comparison of the pre- and post-treatment PD groups in terms of serum GHR levels, lipid profile (TRG, Total-C, LDL-C, HDL-C, and VLDL-C), and BMI

	GHR (pg/mL)	TRG (mg/dl)	Total-C (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	BMI (kg/m^2)
I (n=23)	8.13±4.65	129.78±59.79	183.22±40.03	113.95±30.46	43.91±5.59	28.01±14.68	28.19±3.22
II (n=23)	1.98±1.88	125.48±39.52	122.52±18.92	107.48±18.41	44.65±4.01	23.70±8.19	27.56±3.36
Statistics[a]							
I-II	*p=0.0001**	p=0.73	*p=0.0001**	p=0.37	p=0.62	p=0.20	*p=0.003**

I=Pre-treatment PD group; II=Post-treatment PD group; a= Paired t-test; *: Statistically significant

Table 4. The comparison of the pre- and post-treatment PD with agoraphobia groups in terms of serum GHR levels, lipid profile (TRG, Total-C, LDL-C, HDL-C, and VLDL-C), and BMI

	GHR (pg/mL)	TRG (mg/dl)	Total-C (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	BMI (kg/m^2)
I (n=14)	10.47±4.58	152.29±62.87	196.43±40.36	124.93±30.02	46.29±4.39	30.49±16.74	28.06±2.95
II (n=14)	2.27±2.18	133.21±41.15	125.14±15.19	113.07±20.44	44.50±3.76	22.00±8.36	27.37±3.22
Statistics[a]							
I-II	*p=0.0001**	p=0.28	*p=0.0001**	p=0.27	p=0.22	p=0.08	*p=0.02**

I=Pre-treatment PD with agoraphobia group; II= Post-treatment PD with agoraphobia group; a= Paired t-test;
*: Statistically significant

Table 5. The comparison of pre- and post-treatment PD without agoraphobia groups in terms of serum GHR levels, lipid profile (TRG, Total-C, LDL-C, HDL-C, and VLDL-C), and BMI

	GHR (pg/mL)	TRG (mg/dl)	Total-C (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	BMI (kg/m^2)
I (n=9)	4.49±0.92	94.78±33.80	162.67±31.27	96.89±23.41	40.22±5.43	24.16±10.50	28.40±3.78
II (n=9)	1.55±1.26	113.44±35.73	118.44±24.05	98.78±10.62	44.89±4.60	26.33±7.62	27.87±3.77
Statistics[a]							
I-II	*p=0.01**	p=0.21	*p=0.008**	p=0.59	p=0.06	p=0.31	p=0.08

I=Pre-treatment PD without agoraphobia group; II=Post-treatment PD without agoraphobia group;
a=Wilcoxon Signed Rank Test; *: statistically significant

When the pre- and post-treatment PD without agoraphobia groups were compared in terms of the same parameters, only the serum GHR and Total-C levels in the post-treatment PD without agoraphobia group were statistically significantly lower than in the pre-treatment group (p=0.01 and p=0.008, respectively), and there was no significant difference between the two groups in terms of TRG, LDL-C, HDL-C, VLDL-C levels, or BMI (p=0.21, p=0.59, p=0.06, p=0.31, and p=0.08, respectively) (Table 5).

When the pre-treatment subgroups of PD with or without agoraphobia were compared according to the scale scores and the number of weekly attacks, PAS total and HAM-A scores in the PD with agoraphobia group were statistically significantly higher than the PD without agoraphobia group (p=0.006, p=0.0001, and p=0.004, respectively), yet no statistically significant difference was found between the two groups in terms of HAM-D scores (p=0.54).

When the pre- and post-treatment PD groups were compared according to the scale scores and the number of attacks, PAS total, HAM-A scores, and number of attacks in the pre-treatment PD group were statistically significantly higher than the post-treatment PD group (p=0.001, p=0.0001, and p=0.0001, respectively), yet no statistically significant difference was found between the two groups in terms of HAM-D scores (p=0.26).

When the correlations between the serum GHR levels, lipid profiles (TRG, Total-C, LDL-C, HDL-C, and VLDL-C), BMI, age, number of attacks per week, and the administered scales (PAS Total, HDRS, HARS) in the pre- and post-treatment PD groups were evaluated, there was a significant positive correlation between the serum GHR levels and TRG, PAS Total, and number of attacks per week in the PD pre-treatment group ($p<0.05$). There was a significant negative correlation between serum GHR levels and HDL-C in the post-treatment PD group ($p<0.05$) (Table 6).

Table 6. Correlation analysis between serum GHR levels and other variables in the pre- and post-treatment PD groups

	Pre-treatment PD GHR (n=53) (r, p)	Post-treatment PD GHR (n=23) (r, p)
TRGa	(0.291, 0.03*)	(-0.019, 0.93)
Total-Ca	(0.052, 0.71)	(-0.221, 0.31)
LDL-Ca	(0.123, 0.38)	(-0.204, 0.35)
HDL-Ca	(0.086, 0.54)	(-0.416, 0.04*)
VLDL-Ca	(0.004, 0.98)	(-0.283, 0.19)
BMIa	(0.201, 0.15)	(-0.055, 0.80)
PAS Totala	(0.569, 0.0001*)	(0.153,0.48)
Agea	(0.242, 0.08)	(0.334,0.12)
Number of attacksa	(0.355, 0.009*)	-
HDRSa	(-0.003, 0.98)	(-0.034,0.88)
HARSa	(0.121, 0.39)	(-0.186,0.40)

*: Statistically significant, a: Pearson correlation tests were used

DISCUSSION

Aminergic neurotransmitters control appetite with their effects at the hypothalamic level (Kalra et al. 1999). Some of these substances are GHR, leptin, orexin A, orexin B, cocaine, and peptide or neuropeptide hormones, such as the amphetamine-regulated transcript peptide (CART). These hormones affect hypothalamic dopamine, noradrenaline (NA), and serotonin release at different levels (Brunetti et al. 1999). The anorectic effects of amphetamines are explained with the inhibition of dopamine re-uptake in the lateral hypothalamus (Samanin & Garattini 1993). Peptides such as orexin A and orexin B that stimulate the appetite are reported to suppress the release of serotonin at the hypothalamic level. These effects are thought to contribute to their roles in stimulating the appetite (Brunetti et al. 2002). Leptin is said to inhibit the release of hypothalamic NA in an acute way and this inhibition may play a role in the anorectic effect (Wellman et al. 1993, Brunetti et al. 1999). The appetite-stimulating effect of GRH may be regulated by the suppression of serotonin and hypothalamic dopamine release (Samanin & Garattini 1993, Brunetti et al. 2002). The interaction of many neurotransmitters that play important roles in the etiopathogenesis of psychiatric disorders, such as dopamine, serotonin, and NA with these peptide or neuropeptide hormones, has been a focus of attention in the last couple of years. GHR decreases serotonin release and influences its levels, suggesting that GHR and serotonin interact in the central nervous system (Wellman et al. 1993, Brunetti et al. 2002). GHR levels, during fasting, were reported to be associated with insulin and cholesterol levels (Purnell et al. 2003). Studies on GHR in anxiety disorders are limited in the literature. In this study, the serum GHR, TRG, Total-C, LDL-C, and VLDL-C levels in the PD with agoraphobia group were significantly higher than the PD without agoraphobia and control groups. When the PD without agoraphobia group was compared with the control group, no statistically significant difference was found between the two groups in terms of serum GHR and lipid profile. It was reported that the decrease in serotonergic activity plays a role in antisocial personality disorder, impulse control disorders, and impulsivity and suicidal behaviour and that anxiety is associated with the serotonergic system (Roy & Linnoila 1988, Bell & Nutt 1998, Bayraktar 2008). In addition to the relationship of GHR with serotonergic system-related anxiety, GHR also affects corticotrophin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) at the hypothalamic-pituitary level. GHR affects ACTH release by stimulating CRH directly, but stimulates CRH release as a response to the activated noradrenergic system and reportedly decreased CRF release in PD (Nemerof et al. 1990, Wren et al. 2002). This information suggests that GHR is associated with anxiety through CRF by serotonin and at the hypothalamic-pituitary level. Additionally, GHR administration increased adipogenesis and adiposity (Barazzoni et al. 2006). One study suggests that GHR functions as an adiposity signal, a messenger between the body's energy stores and the brain (Schwartz et al. 2000). As seen in our results, there is a complicated relationship between GHR, serum lipids, and PD with agoraphobia, a disorder where anxiety is experienced intensively.

Agoraphobia in PD is reported to increase the severity of the disease (Kocabasoglu 2002, Bayraktar 2008). In this study, a higher weekly number of attacks, PAS total, and HARS scores in those with agoraphobia, when compared to those without agoraphobia, supports that agoraphobia increases the severity of PD. In this study, high serum GHR levels in the PD group with agoraphobia might be related to the severity of illness; this could be accomplished by suppressing serotonergic activity. Additionally, not having a difference between the groups in terms of BMI may indicate that the increase in serum GHR levels cannot be explained by factors such as appetite or eating behaviour. Neurobiological differences can be utilized together with clinical signs in the distinction of PD subgroups with and without agoraphobia; however, our findings must be supported by additional studies with larger patient groups.

Investigation of the relationship between high serum lipids and psychiatric disorders started in the 1990s. Changes in neuronal lipid concentration impaired transmission, particularly at serotonergic neurons and at the receptor level (Davidson et al. 1996). Increased noradrenergic stimulation may elevate serum lipid levels by activating lipoprotein lipase in PD (Bajwa et al. 1992). On the other hand, it is said that decreased plasma cholesterol levels may disrupt neural membrane fluidity and disrupt many functions, including serotonergic transmission (Hawton et al. 1993). In many studies, high serum lipid levels in patients with PD were reported (Bajwa et al. 1992, Reifman & Windle 1993, Fredman et al. 1995, Agargün et al. 1996, Yamada et al. 1997). Agargün et al. (2004) found a positive correlation between panic attacks and high serum lipid levels. The serum lipid levels in the OCD group without panic attacks were no different than the control group in this study. The presence of "fear of death" was associated with high levels of cholesterol in patients diagnosed with PD in another study (Shioiri et al. 2000). In our study, the PD with agoraphobia group's serum lipids, except HCL-C, were higher than in the control group. When the relationship between the severity of anxiety and serum lipids are taken into account, the addition of agoraphobia to PD may increase the severity of the disease and serum lipids further.

We started paroxetine, a SSRI group antidepressant, at 20-40 mg/day for PD patients and re-evaluated the serum GHR and lipid profile at the end of 12 weeks. The remaining 30 patients were excluded from the study because they did not come regularly to their outpatient

follow-up and did not regularly use paroxetine. These results highlight the critical importance of devising effective treatment strategies to enhance PD patients' adherence to medications. Low persistence and poor compliance to antidepressant treatment were problematic in patients with depression in the clinical outpatient setting of one study (Sawada et al. 2009). Furthermore, a positive effect of the use of benzodiazepine-derivative anxiolytics on the persistence to antidepressant treatment was found at month 1 to this study (Sawada et al. 2009). Considering this information, including only patients taking paroxetine to our study may have been reduced the compliance with treatment. At the end of 12th week, 23 of 53 patients continued the treatment, and these patients could be evaluated after the treatment.

Evaluation of the serum GHR, Total-C levels, and BMI of 23 patients who completed the treatment showed a significant decrease after treatment. TRG, LDL-C, and VLDL-C levels also decreased after treatment, but this was not statistically significant. When the PD with agoraphobia group was compared before and after the treatment in terms of the same parameters, a significant decrease in the PD with agoraphobia group was again seen after the treatment in terms of serum GHR, Total-C levels, and BMI. A significant decrease was found only in serum GHR and Total-C levels in the PD without agoraphobia group after the treatment. A significant decrease was found in serum GHR and LDL-C levels in a study on patients with MD that compared serum GHR and lipid profile before and after citalopram (SSRIs) use (Barim et al. 2009). In another study, antidepressant therapy was administered to patients diagnosed with PD and MD. Later, the PD and MD groups that responded to treatment, PD and MD groups that did not respond to treatment, and the control group were compared in terms of serum GHR levels. Serum GHR levels were higher in the MD group that did not respond to treatment than the MD group that responded to treatment and control group and higher in the PD group that did not respond to treatment than the control group. The study reported that serum GHR levels decrease with the maximum therapeutic effect of antidepressant treatment (Ishitobi et al. 2012). In our study, we found that the number of attacks, PAS total, HAM-A scale scores, Total-C, BMI, and serum GHR decreased significantly in the post-treatment group; exclusion of patients with a history of drug use that can affect the lipid profile increases the reliability of our results. These results suggest that SSRIs decrease GHR levels by increasing the amount of serotonin in the synaptic cleft.

The correlation analysis showed a positive correlation between serum GHR levels, the PAS Total score, and the weekly number of attacks in the pre-treatment PD group, indicating that serum GHR levels increase as the severity of the disease increases. The lack of the same positive correlation in the post-treatment group may be due to having fewer patients who continued with the treatment. In the post-treatment PD group, the negative correlation between serum GHR levels and levels of HDL-C, known as protective cholesterol, may ensure cardiovascular protection in PD patients (Maes et al. 1997, Eren et al. 2012). When the relationship between neuronal lipid concentrations and serotonergic neurons at the receptor level is taken into account, the regulation of blood lipid profile with treatment may improve PD symptoms.

There is a growing interest in the role of neurotrophins in the pathophysiology of psychiatric disorders (Martinotti et. al. 2012). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. It is a dimeric protein thought to be involved in neuronal survival and synaptic plasticity, and to be an important biomarker for psychiatric conditions such as depression, anxiety disorders, and bipolar disorder. In studies on this topic, neurotrophins like BDNF are reported to be a useful determiner in diagnosis and prognosis of various psychiatric disorders (Angelucci et al. 2014). BDNF contributes the same mechanism with leptin in regulating lipid metabolism and metabolic parameters (Boyuk et al. 2014). This information makes us think that there may be a pathophysiological relationship between neurotrophins (such as BDNF) and aminergic neurotransmitters (such as GHR, leptin), and lipid metabolism. However, new studies are needed on this topic.

CONCLUSIONS

Given these results, a pathophysiological relationship may be present between serum GHR levels and the lipid profile in PD with agoraphobia. In addition, because the relationship is more evident in the group with agoraphobia than without agoraphobia, there may be a neurobiological differentiation between the groups. However, due to the exclusion criteria of our study, the small number of our group does not enable us to generalize our results. There is a need for further studies with larger groups of patients with agoraphobia; our results need to be assessed in the light of more comprehensive and detailed studies.

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