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Title: The role of depression in obesity and the relationship between cognitive functions, leptin, ghrelin, and neuropeptide Y.

Short titile: Obesity and depression; cognitive functions and neurochemical parameters.

Abstract

Purpose: It is known that there is a two-way relationship in the etiopathogenesis of depression and obesity. This study aimed to investigate serum ghrelin, leptin, neuropeptide Y levels, cognitive functions, and atypical depressive features in obese and depressed patients. It is expected that obese and depressed patients will show similar features in terms of biochemical parameters and cognitive functions, and atypical depressive features may be high in obese individuals.

Materials and methods: The study included 56 obese individuals, 60 patients with major depressive disorder (MDD), and 53 healthy controls (HC). The questionnaires administered included socio-demographic data form, Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Dutch Eating Behaviour Questionnaire, Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder Version (SIGH-SAD). Cognitive functions were assessed with short computer version of Wisconsin Card Sorting Test (WCST), Berg's WCST, Stroop Colour-Word Test-Victoria version. Serum ghrelin, leptin, and neuropeptide Y levels were measured.

Results: The depression scores were found higher MDD group than obesity and HC groups (p<0.001) and anxiety scores similar in MDD and obesity groups (p=0.064). The groups had similar mean SIGH-SAD scores (p=0.989). There was no difference between groups in WCST scores (p>0.05). Differences were detected between the groups in the Stroop test. Leptin levels were higher (p<0.001), ghrelin (p=0.038) and neuropeptide Y (p<0.001) levels lower in obesity group compared to MDD and HC. Ghrelin levels negatively correlated with total number of incorrect responses in terms of cognitive functions in obese individuals (r=-0.259 p=0.049).

Conclusion: In our study, it was determined that although depressive symptoms were high in obesity, there were no atypical depressive features, executive functions were similar between the groups, and neurochemical marker levels were not similar in obesity and depression. Our results do not support the relationship between obesity and atypical depression.
Keywords: Obesity, depression, cognitive functions, leptin, ghrelin, neuropeptide Y.

Makale başlığı: Obezitede depresyonun rolü ve bilişsel işlevler, leptin, ghrelin, nöropeptid Y ilişkisi.

Kısa başlık: Obezite ve depresyon; bilişsel işlevler ve nörokimyasal parametreler.

Öz

Amaç: Depresyon ve obezite etyopatogenezinde karşılıklı iki yönlü bir ilişkinin olduğu bilinmektedir. Bu çalışmada, obezite ve depresyon hastalarında serum ghrelin, leptin, nöropeptid Y düzeylerinin, bilişsel işlevlerin ve atipik depresif özelliklerin araştırılması amaçlanmıştır. Nörokimyasal parametreler ve bilişsel işlevler açısından obezite ve depresyon hastalarının benzer özellikler göstereceği ve obez bireylerde atipik depresif özelliklerin yüksek olabileceği beklenmektedir.

Gereç ve yöntem: Çalışmaya 56 obez birey, 60 major depresif bozukluklu (MDB) hasta ve 53 sağlıklı kontrol alınmıştır. Sosyodemografik veri formu, Hamilton Depresyon Derecelendirme Ölçeği (HAM-D), Hamilton Anksiyete Ölçeği (HAS), Hollanda Yeme Davranışı Anketi, Yapılandırılmış Görüşme Kılavuzu Mevsimsel Duygudurum Bozukluğu Versiyonu (SIGH-SAD) uygulanmıştır. Bilişsel işlevler Wisconsin Kart Eşleme Testi'nin (WCST) kısa bilgisayar versiyonu Berg's WCST, Stroop testinin Victoria formu olan Victoria Stroop Test ile değerlendirilmiştir. Serum ghrelin, leptin, nöropeptid Y düzeyleri belirlenmiştir.

Bulgular: MDB grubunda depresyon puanları obezite ve sağlıklı kontrol grubuna göre yüksek (p<0.001), MDB ve obezite gruplarında anksiyete puanları benzer (p=0.064) bulundu. SIGH-SAD puan ortalamaları açısından gruplar arasında fark bulunmadı (p=0.989). Gruplar WCST puanları açısından da benzerdi (p>0.05). Stroop testinde gruplar arasında farklılık tespit edildi. Leptin düzeyleri obezite grubunda diğer gruplardan yüksekti (p<0.001), ghrelin (p=0.038) ve nöropeptid Y (p<0.001) düzeyleri ise düşük bulundu. Obez bireylerde ghrelin düzeyleri ile bilişsel işlevler açısından toplam yanlış cevap sayısı arasında negative yönde zayıf düzeyde korelasyon saptandı (r=-0.259 p=0.049).

Sonuç: Çalışmamızda obezitede depresif belirtilerin yüksek olmasına karşın atipik depresif özellikler bulunmadığı, gruplar arasında yürütücü işlevlerin benzer olduğu, obezite ve depresyonda nörokimyasal belirtileç düzeylerinin benzer olmadığı belirlenmiştir. Sonuçlarımız obeziteyi atipik depresyon ilişkisini desteklememektedir.
Anahtar kelimeler: Obezite, depresyon, bilişsel işlevler, leptin, ghrelin, nöropeptid Y.

Introduction

The most common psychiatric disorder is depression and it is known that obesity is high in depression, and depression and the prevalence of depressive symptoms are high in obesity [1, 2]. Increased appetite and reduced physical activity due to depression, the appetite boosting side effects of medications used, and binge eating during depression facilitate development of obesity [3]. While loss of weight and appetite is observed in classical depression resulting in decreased body weight, there is increased appetite and weight in “atypical depression”, which is a subtype of depression. The atypical subtype of depression is diagnosed in the presence of mood reactivity accompanied by two of the following characteristics; hypersomnia, leaden paralysis, increased appetite/weight gain, and a long-lasting interpersonal rejection sensitivity. It has been argued that obesity can be a clinical manifestation of atypical depression [3-5]. There are studies suggesting that obesity is a clinical manifestation of atypical depression progressing with increased appetite and finding association between atypical depression and a high BMI [6-8].

The role of parameters such as ghrelin, leptin, and neuropeptide Y in both obesity and depression has attracted more attention in the recent years. Having appetising and adipogenous properties, ghrelin increases anxiety and depression-like behaviours [9]. Leptin increases energy consumption and diminishes appetite. Ghrelin antagonises the anorexigenic effect of leptin by means of hypothalamic neuropeptide Y/Y1 (NPY) receptor. Thus, there is a metabolic antagonism between leptin and ghrelin with respect to their functions in the body [9]. Leptin shows a negative correlation with depression and anxiety independent of body fat and weight; it is argued that the anti-depressive effects of leptin vanishes due to leptin resistance in obese individuals [9]. NPY is the major peptide stimulating food intake and has an anxiolytic effect [10]. Known to play an important role in responding stress and psychiatric disorders, NPY is also a major mediator of emotional eating [11, 12]. The relationships of these three parameters with obesity are clear, but their relationships with depression is not so apparent.

Depression and obesity have negative impact on cognitive functions. Depression is known to involve attention and memory problems and impairment of executive functions [13, 14]. It has been reported that in obesity there is frontal/subcortical function deficiency; with increased Body Mass Index (BMI), cognitive functions deteriorate and impairment occurs in cognitive flexibility, inhibition capacity, working memory, decision making, verbal fluency, and planning [15]. It is not clear whether increased fat is a cause or result of impairment in cognitive functions. Worsened cognitive skills, increased impulsiveness, decreased inhibition capacity are likely explanations for excessive eating, binge eating, and loss of eating control [16, 17]. Conversely, a recent meta-analysis has concluded that there is no cognitive function impairment in obesity [18]. It can be thought that cognitive functions may provide guidance in understanding the relationship between obesity and depression.

This study aimed to investigate the relationship between obesity and depression in a multifaceted manner. In this context serum ghrelin, leptin, neuropeptide Y levels, and executive functions were examined in obese and depressed patients, and the two groups were compared in terms of atypical depressive features. It is expected that the two groups will be similar in terms of biochemical parameters and cognitive functions, and atypical depressive features will be high in obesity.

Materials and methods

Participants

The study included 60 patients who presented to the Psychiatry outpatient clinic of Pamukkale University Medical School Hospital between December 2018 and September 2019 and who were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) and 56 patients who presented to the Endocrinology outpatient clinic of the Endocrinology and Metabolism Department of the University Hospital and were diagnosed with obesity with a BMI of 30 kg/m^2 and above. The healthy control group consisted of 53 individuals who had no MDD or obesity diagnosis and had similar characteristics to the patient groups in terms of age and gender. The healthy control group was formed from the hospital staff who volunteered upon announcement of the study. The ages of participants ranged between 18 and 65. Patients with other psychiatric disorders (schizophrenia, mental retardation, bipolar disorder) and those with a neurological disease leading to a cognitive function disorder (cerebrovascular disease, dementia) were excluded from the study. The subjects were informed about the study and their verbal and written consents were obtained before inclusion.

This research project was approved by the Ethics Committee of Pamukkale University with their decision dated 14/11/2018 and numbered 60116787-020/77483. The study was also supported by the Scientific Research Projects Coordination Unit of Pamukkale University with their decision numbered 2018TIPF047.

Procedures

The participants were administered a psychiatric examination to explore the presence of a psychiatric disorder according to the DSM-5 criteria. Weight, height, waist circumference, and blood pressure measurements were carried out to explore presence of metabolic syndrome according to the NCEP-ATP III diagnostic criteria [19]. Abdominal obesity (waist circumference ≥102 cm in males and ≥88 cm in females), triglyceride (TG) (≥150 mg/dl or receiving pharmacological treatment for high TG), high-density lipoprotein (HDL) (<50 mg/dl in females and <40 mg/dl in males or receiving pharmacological treatment for low HDL), blood pressure (≥130/85 mmHg or receiving anti-hypertensive treatment), and fasting blood sugar (≥100 mg/dl or receiving treatment for high blood sugar) were considered for a metabolic syndrome diagnosis. The fasting blood sugar, TG, and HDL values were obtained from the endocrinology outpatient clinic records. A questionnaire prepared by the investigator questioning socio-demographic data and clinical characteristics was filled out and neuropsychological assessments were completed.

Psychometric assessment

Hamilton Depression Rating Scale (HAM-D)

It is a 17-item scale developed to assess severity of depression [20]. A total score between 0 and 53 is obtained with higher scores indicating increased severity of depression. Scores 0-7 indicate no depression, 8-15 mild, 16-28 moderate and 29 and above severe depression. The scale was tested for validity and reliability in Turkish [21].

Hamilton Anxiety Rating Scale (HAM-A)

It was prepared to find the level of anxiety and symptom distribution and to measure changes in severity [22]. It consists of 14 items questioning mental and physical symptoms. A total score of 17 and less is rated as mild, between 18 and 24 as moderate, and 25 and above as severe anxiety. It was tested for validity and reliability in Turkish [23].

Structured Interview Guide for Hamilton Depression Rating Scale-Seasonal Affective Disorders Version (SIGH-SAD)

It is a structured interview guide designed to standardize the use of HAM-D and to cover the entire symptoms of depression [24]. This interview guide was constructed by adding 8 items prepared by Rosenthal for atypical depression to the 21-item form of

HAM-D. The atypical balancing score is shown as a percentage by dividing the scale score by the total 29-item SIGH-SAD score and multiplying it by 100. Its Turkish version was tested for validity and reliability [25].

Dutch Eating Behaviour Questionnaire (DEBQ)

Besides internal eating behaviours such as hunger, the questionnaire was developed also to reveal other external factors that affect eating. It consists of 3 subscales; restrained eating, emotional eating, and external eating. It is a 5-point Likert-type self-reporting scale consisting of 33 items [26]. The scale was tested for validity and reliability in Turkish [27].

Neuropsychological assessment

Wisconsin Card Sorting Test

The Psychology Experiment Building Language (PEBL)-Berg's "Wisconsin" Card Sorting Test (WCST), which is the short computer version of the Wisconsin Card Sorting Test, was administered to measure frontal lobe functions and executive functions [28]. This test evaluates an individual's problem-solving ability and ability to change his/her problem-solving strategy according to changing circumstances. WCST measures cognitive processes such as complex (executive) attention, perseveration, working memory, executive functions, concept formation, and abstract reasoning. When the classical application was compared to the short computer version involving 64 response cards, the results of both applications were reported to be similar [29]. The responses given by the subject until the application ends are recorded by the computer and the subject's test performance score is calculated by the existing program at the end of the test.

Stroop Test

The Psychology Experiment Building Language (PEBL)-Victoria Stroop Test, which is the Victoria form of the Stroop Test, was administered to assess selective attention, focused attention, response inhibition, interference control, cognitive flexibility, and information processing rate [28]. The Stroop test is said to reflect three basic processes; selective attention, reading, and colour telling [30]. The scoring method in the Stroop Test Victoria Form involves simple measurements of time used to complete the parts. The time it took to complete each part and the number of errors were recorded automatically in a PEBL file with a participant code. While the first and second parts of the test were used to measure cognitive rate, the third part was used to measure response inhibition. The computer program (PEBL) based management of the test required the participant in the case of an error to correct that error before continuing with the next item and this to

be reflected in the completion time of the test. Longer times indicate impairment of attention.

Biochemical Assessment

After 12 hours of fasting, 10 cc of venous blood was taken from the antecubital vein of each participant in the case and control groups into a biochemistry tube. After the samples were kept at room temperature for approximately 20 minutes, they were centrifuged at 5000 rpm for 10 minutes and the samples obtained were stored at -80°C for biochemical analysis to determine leptin, ghrelin and neuropeptide Y levels. Biochemical parameters were measured by ELISA method.

Statistical analysis

The data were analysed using the SPSS 25.0 (IBM SPSS Statistics 25 software Armonk, NY: IBM Corp.) package program. The continuous variables were expressed as means ± standard deviations and medians (smallest-largest values) and the categorical variables as numbers and percentages. Compliance of the data with a normal distribution was explored with the Kolmogorov Smirnov and Shapiro Wilk tests. When the parametric test assumptions were met, the differences in independent groups were compared using the Significance of Difference Between the Means of Two Groups Test and One-Way Variance Analysis (Post hoc: “Tukey Test”). When the parametric test assumptions were not met, the independent group differences were compared using the Mann Whitney U test and Kruskal Wallis Test (Post hoc: "Bonferroni-Corrected Mann Whitney U test"). The relationship between the numeric variables were assessed with the Spearman correlation analysis. The differences between the categoric variables were analysed with the Chi-square Analysis. In all analyses, $p<0.05$ at 95% confidence interval was considered statistically significant.

Results

Socio-demographic data and scale results

The study included 56 subjects diagnosed with obesity, 60 patients diagnosed with MDD and 53 healthy controls. The participants’ socio-demographic data and scale scores are shown in Table 1 and their health indicators in Table 2. Depression scores were higher in the MDD group than in the obesity and healthy control groups, but no difference was found between the anxiety scores of the MDD and obesity groups. No difference was found between the MDD and obesity groups with respect to their mean SIGH-SAD scores, which measure atypical depression (Mann-Whitney U test $p=0.945$, $z=-0.069$). The emotional eating score was higher in the obesity group than in the other two groups. Thirty individuals (53.5%) in the obesity group were satisfying the MDD diagnostic criteria

when they joined the study. No difference was found between the depressive patients in the obesity group and the MDD group with respect to their SIGH-SAD scores (p=0.456, z=-0.745, Mann-Whitney U test).

Neuropsychological assessment

While the groups were found similar with respect to their WCST scores, the obesity group showed a poorer performance than the control group in the Stroop test (Table 3). No significant difference was found in the cognitive functions of the individuals in the obesity group with and without a metabolic syndrome diagnosis (p>0.05, Mann-Whitney U test).

Data on parameters of leptin, ghrelin and neuropeptide Y

The leptin levels were found higher and the ghrelin and neuropeptide Y levels lower in the obesity group compared to the other groups (Table 4). The relationships between the neuropsychological tests and the BMI, HAM-D, HAM-A, and biochemical parameters are presented in Table 5 and Table 6. A moderate positive correlation was found in the MDD group and a positive low correlation in the obesity group between the HAM-D, HAM-A scores and the Stroop Part D, Stroop Part W, Stroop Part C times (p>0.05 for all). In the control group, a moderate positive correlation was found between the mean BMI and the mean Stroop Part D, Stroop Part W, and Stroop Part C times.

Discussion

Our study aimed to examine the two-way relationship between obesity and major depressive disorder and to seek an answer to the question of whether a subgroup of obesity patients has undiagnosed depression (especially atypical depression). MDD ratio was 53.5% in the obesity group, but it did not differ from the depression group with respect to the characteristics of atypical depression. The prevalence of MDD was higher in the obesity group than in the control group. Our results strongly support the comorbidity of obesity and depression as in the previous studies [2, 31]. A meta-analysis has found that BMI was 2.55 times higher in atypical depression subtype than in melancholic subtype. It has been stressed that obesity seen in depression may be associated with atypical subtype of depression and it deserves clinical investigation [32]. Atypical depression was found to be accompanied by female gender, unhealthy behaviours (smoking, social isolation, decreased physical activity, etc.), and psychiatric comorbidities as well as obesity, cardiovascular diseases, and metabolic syndrome [33]. A study exploring the causal relationship between obesity and depression found correlation between BMI and increased appetite, but no causal relationship was found when the other atypical symptoms were investigated as a whole [34]. Our results also

suggest that the comorbidity of depression is high in obesity, but it does not qualify as a characteristic for atypical depression subtype. This subject requires long-term follow-up studies with larger patient groups.

Emotional eating scores

Emotional eating scores were found higher in the obesity group than in other groups. The high rate of emotional eating in the obesity group may be related to the high rate of depressive symptoms in this group. Obesity was found higher in individuals who have a higher level of emotional eating and find it difficult to control themselves [7]. It has been argued that emotional eating is associated with body weight, obese individuals eat more in negative emotional states than those with a low or normal weight, and eating increases the level of anxiety [35]. A meta-analysis found that the restrained, uncontrolled and emotional eating scores of obese people were higher than those of individuals with a normal weight and BMI showed a positive correlation with emotional and uncontrolled eating [36]. Available data suggest that learning methods to express negative emotions and to cope with these emotions would be beneficial in fighting with obesity in individuals who exhibit emotional eating behaviours.

Cognitive functions

In our study, no difference was found between the groups with respect to executive functions. While the healthy control group showed the best performance in selective attention, focused attention, response inhibition, interference control, and information processing rate, the performance of the obesity group was found the lowest. It was determined that as BMI increased, cognitive function performance decreased in the control group. As depression and anxiety symptoms increased, their performance in the attention test declined in the obesity and MDD groups. Our findings indicate that executive function and attention performances are similar between obesity and depression and do not differ from the healthy control group. In the healthy control group, cognitive performance decreases as weight increases. These findings are similar to previous studies [37-40]. New studies are needed to understand the relationship between weight gain and cognitive functions.

Biochemical parameters

In our study, the highest serum leptin value was found in the obesity group and the lowest in the MDD group. Studies have found a strong correlation between high leptin levels and the atypical subtype of MDD (in the present and recovered patients). In patients who were currently in an episode, high leptin levels were found associated with hyperphagia, weight gain, and leaden paralysis, which are characteristic features of atypical depression. This relationship was found to indicate a leptin resistance caused by

increased fatty tissue. This relationship has not been observed with the other subtypes [41]. Plasma and cerebrospinal fluid leptin levels were found to decrease in patients with anorexia nervosa (AN). It has been shown that the changes in leptin levels disappear when the body weight returns to normal and the plasma and CSF leptin levels of recovered AN patients are similar to the control values in the long run [42]. Hippocampal leptin deficiency is argued to cause obesity-induced depression and leptin has antidepressant effects [43]. In a study made with women with eating spectrum disorder, serum leptin levels showed a negative correlation with depression and anxiety independent of body fat and weight, and leptin's antidepressant effects disappeared due to leptin resistance in obese people [9]. Severely obese individuals can be resistant to the effects of leptin; the increased serum leptin levels in these individuals are often seen as an indication of leptin resistance [44]. Previous studies support weight gain associated with atypical depressive features and leptin resistance. In our study, leptin levels may have been low in the depression group due to the lack of atypical depressive features in the obesity and depression groups. Follow-up studies on both obesity and depression and comparison studies after weight loss and depression recovery are needed in this area.

The highest mean ghrelin value was found in the MDD group and the lowest in the obesity group. Ghrelin has appetising and adipogenous effects [45]. While ghrelin levels have been found low in obese individuals, they have been found high in those diagnosed with AN [46]. Ghrelin has been found to inhibit hypothalamic serotonin release and to activate hypothalamic pituitary adrenal axis, which can aggravate anxiety and depression symptoms [9, 47]. High level of ghrelin found in the MDD group in our study is consistent with the studies in the literature reporting depressive symptom-increasing properties of ghrelin. Some studies have linked better cognitive functions to high serum ghrelin levels and found that the plasma concentration of this hormone decreases in older individuals and Alzheimer's patients [44]. Our results are consistent with those of the studies that link better cognitive functions to high serum ghrelin levels [44, 48]. A borderline positive relationship was found between ghrelin and cognitive functions in the obesity and control groups.

The obesity group had the lowest mean neuropeptide Y value. It is known to play an important role in the response to stress and psychiatric disorders; it is potentially a major mediator of "emotional eating" [49]. NPY is known to be the strongest endogenous substance showing an antagonist effect on the behavioural outcomes of anxiety and stress [11]. The risk of anxiety and depressive disorder was found high in individuals whose NPY levels were low in their peripheral NPY measurements [12]. NPY has been

shown to enhance neuroprotection, stimulate neurogenesis, and alleviate neuroinflammation [50]. No correlation was found in our study between serum NPY levels and depression or anxiety. However, a positive correlation was found between the serum neuropeptide Y levels and the WCST learning to learn scores in the control group.

The study may contribute to the literature by examining the two-way relationship between obesity and depression in terms of emotional eating and cognitive functions and by trying to predict this with biochemical parameters associated with obesity. One of the limitations of this study is that the education levels of the healthy subjects included in the study were statistically significantly higher compared to the patient group. Neurocognitive tests are influenced by education. It can be said that weight control is achieved better as the level of education goes up. The prevalence of metabolic syndrome was higher in the obesity group than in the other groups due to the accompanying physical diseases. Not excluding these diseases is another limitation of our study; accompanying physical diseases may have influenced the levels of depression and anxiety. In addition, the fact that the effects of the antidepressants used on neurochemical parameters were not examined is a limitation of our study and should be taken into consideration when evaluating our results.

Our results show that emotional eating behavior scores are higher in the obesity group, executive dysfunction is not seen in the obesity group, but executive dysfunction may be seen as depression and anxiety symptoms increase, selective and sustained attention is impaired in the obesity group, this impairment may increase as depression and anxiety symptoms increase, leptin resistance is present in the obesity group, serum ghrelin has the feature of increasing depressive symptoms, ghrelin may be associated with good cognitive function level. Our study indicates that the obesity group does not show a significant feature in terms of atypical depression subtype, but obesity and depression comorbidity are high, and these individuals should definitely be evaluated for depression.

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Authors contributions: O.K., G.V. and Y.E. have constructed the main idea and hypothesis of the study. O.K., G.V. and Y.E. developed the theory and arranged the material and method section. O.K. G.V., T.U. O.T. and M.G. have done the evaluation of the data in the Results section. O.K. and G.V. have written the discussion section of the article. G.V., T.U., O.T. and M.G. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Conflict of interest: No conflict of interest was declared by the authors.

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Table 1. Socio-demographic data and scale scores of the groups

	Obesity Mean±SD	**MDD Mean±SD**	**Control Mean±SD**	***p****	***p1****	***p2****	***p3****	**χ^2**
BMI	35.26±4.88	23.75±3.42	24.01±3.49	**<0.001**	**<0.001**	**<0.001**	1.000	111.76
Age	39.02±8.41	36.57±12.12	35.6±7.65	0.080	-	-	-	5.057
Education year	10.8±5.46	11.82±5.11	16.02±5.3	**<0.001**	0.904	**<0.001**	**<0.001**	26.814
HAM-D	10.23±8.07	16.33±7.46	2.26±2.04	**<0.001**	**<0.001**	**<0.001**	**<0.001**	88.609
HAM-A	17.2±13.28	21.55±12.18	7.47±6.45	**<0.001**	0.064	**<0.001**	**<0.001**	42.780
SIGH-SAD	23.65±23.53	20.87±11.15	28.36±33.1	0.989	-	-	-	0.022
DEBQ-Restrained	14.32±9.71	13.53±11.6	13.09±11.59	0.608	-	-	-	0.996
DEBQ Emotional	18.55±17.77	8.88±12.26	10.06±12.18	**0.005**	**0.005**	**0.056**	1.000	10.596
DEBQ-External	13.89±7.47	11.2±9.57	14.13±8.91	0.159	-	-	-	3.676

HAM-D: The Hamilton Rating Scale for Depression, HAM-A: Hamilton Anxiety Rating Scale SIGH-SAD: Structured Interview Guide for Hamilton Depression Rating Scale Seasonal Affective Disorder DEBQ: The Dutch Eating Behaviour Questionnaire, *p*: Obesity-MDD-Control, *p1*: Obesity-MDD, *p2*: Obesity-Control, *p3*: MDD-Control. MDD: Major depressive disorder
BMI: Body-Mass Index, SD: Standard Deviation, χ^2: Chi-squared test, *Kruskal Wallis Test **Mann Whitney U test

Table 2. Clinical characteristics of the groups

Variables		**Obesity n (%)**	**MDD n (%)**	**Control n (%)**	***p****	**χ^2**
Gender	Female	38 (67.9%)	40 (66.7%)	36 (67.9%)	0.987	0.026
	Male	18 (32.1%)	20 (33.3%)	17 (32.1)		
Psychiatric History	Yes	32 (57.1%)	37 (61.7%)	23 (43.4%)	0.133	4.034
	No	24(42.9%)	23 (38.3%)	30 (56.6%)		
Number of MDD Episodes	None	22(39.3%)	0	35 (66.0%)	**<0.001**	64.788
	Single	14(25.0%)	34(56.7%)	17 (32.1%)		
	Multiple	20 (35.7%)	26 (43.3%)	1 (1.9%)		
Family History of Psychiatric Disorder	Yes	18 (32.1%)	23 (38.3%)	14 (26.4%)	0.401	1.827
	No	38 (67.9%)	37(61.7%)	39(73.6%)		
Metabolic Syndrome	Yes	30 (54.6%)	12 (20.0%)	7 (13.2%)	**<0.001**	25.204
	No	26 (46.4%)	48 (80%)	46 (86.8%)		
Comorbid Medical Condition	Yes	19 (33.9%)	20 (33.3%)	14 (26.4%)	0.643	0.882
	No	37 (66.1%)	40 (66.7%)	39 (73.6%)		

*Chi-squared test, MDD: Major Depressive Disorder

Table 3. Neuropsychological test comparisons between groups

	Tests	Obesity Mean±SD	MDD Mean±SD	Control Mean±SD	*p**	χ^2
WCST	**Categories Completed**	2.73±1.48	2.6±1.65	3.13±1.52	0.191	3.309
	Total Correct	41.91±11.43	42.38±11.84	45.08±11.29	0.171	3.527
	Total Errors	22.09±11.43	21.62±11.84	18.36±9.8	0.146	3.842
	Perseverative Responses	19.2±8.86	16.97±10.08	18.79±5.65	0.410	1.785
	Perseverative Errors	9.75±6.03	8.1±6.66	8.68±4.38	0.274	2.588
	Nonperseverative Errors	12.34±13.19	13.52±13.79	9.68±8.69	0.574	1.109
	Conceptual Level Response	35.3±14.71	35.85±15.53	39.57±14.1	0.130	4.076
	Learning to Learn	2.31±8.68	1.49±7.41	-0.79±5.17	0.187	3.348
Stroop Test	**Stroop Part D**	113.22±58.04	102.01±49.98	95.89±64.78	0.123	4.184
	Stroop Part W	84.29±54.09	75.1±37.25	60.25±26.08	**0.041**	6.377
	Stroop Part C	109.09±75.92	89.82±50.49	76.65±53.92	**0.043**	6.303

MDD: Major Depressive Disorder, WCST: Wisconsin Card Sorting Test, Stroop Part D: Dots, Stroop Part W: Neutral Words, Stroop Part C: Color Words, p: Obesity-MDD-Control,
SD: Standard deviation, *Kruskal Wallis test

Table 4. Comparison of serum leptin, ghrelin and neuropeptide Y levels of the groups

	Obese (N=56)	**MDD (N=60)**	**Control (N=53)**	***p****	***p1****	***p2****	***p3****	***F***
	Mean±SD							
Leptin	33.17±21.3	15.36±19.39	18.33±17	**<0.001**	**<0.001**	**<0.001**	0.703	13.317
Ghrelin	168.63±68.67	204.65±78.84	187.47±72.76	**0.038**	**0.029**	0.392	0.446	3.341
NeuropeptideY	0.15±0.04	0.18±0.05	0.18±0.05	**<0.001**	**0.001**	**0.001**	1.000	8.783

MDD: Major Depressive Disorder * ANOVA test, **Tukey Test, *p*: Obesity-MDD-Control, *p1*: Obesity-MDD, *p2*: Obesity-Control, *p3*: MDD-Control

Table 5. The relationship between biochemical parameters with cognitive functions

			Total Correct	Total Errors	Perseverative Errors	Nonperseverative Errors	Learning to Learn	Stroop Part D	Stroop Part W	Stroop Part C
MDD	**Leptin**	r	0.041	-0.041	0.099	-0.027	-0.080	0.069	-0.012	0.101
		p	0.771	0.771	0.477	0.845	0.669	0.620	0.930	0.466
	Ghrelin	r	-0.090	0.090	0.008	0.146	-0.278	0.086	0.081	0.051
		p	0.519	0.519	0.953	0.291	0.130	0.537	0.563	0.716
	Neuropeptide Y	r	-0.213	0.213	0.073	**0.294***	-0.287	0.234	**0.331***	**0.304***
		p	0.121	0.121	0.601	**0.031**	0.118	0.088	**0.014**	**0.025**
Obesity	**Leptin**	r	-0.046	0.046	0.003	0.067	-0.084	0.079	0.092	-0.007
		p	0.732	0.732	0.980	0.616	0.630	0.553	0.494	0.960
	Ghrelin	r	**0.259***	**-0.259***	0.064	-0.255	0.274	-0.209	-0.139	-0.187
		p	**0.049**	**0.049**	0.633	0.053	0.111	0.115	0.299	0.159
	Neuropeptide Y	r	0.085	-0.085	0.095	-0.064	0.123	0.016	0.177	0.113
		p	0.526	0.526	0.478	0.631	0.482	0.903	0.183	0.398
		p	0.146	0.146	0.339	0.309	0.279	0.290	0.254	0.399
Control	**Leptin**	r	0.109	-0.111	0.040	-0.111	0.083	0.016	0.062	0.102
		p	0.448	0.437	0.783	0.437	0.648	0.910	0.665	0.478
	Ghrelin	r	-0.027	0.039	0.060	0.056	**0.374***	-0.131	-0.161	-0.049
		p	0.852	0.787	0.675	0.696	**0.032**	0.358	0.258	0.732
	Neuropeptide Y	r	0.024	-0.035	0.064	-0.019	**0.403***	-0.156	-0.161	-0.108
		p	0.870	0.805	0.654	0.894	**0.020**	0.275	0.260	0.451

Spearman Correlation Analysis, Stroop Part D: Dots, Stroop Part W: Neutral Words, Stroop Part C: Color Words

Table 6. The relationship between scale scores and BMI with cognitive functions

			Total Correct	Total Errors	Perseverative Errors	Nonperseverative Errors	Learning to Learn	Stroop Part D	Stroop Part W	Stroop Part C
MDD	**HAM-D**	r	-0.017	0.017	**-0.359****	0.214	**-0.480****	**0.427****	**0.447****	**0.395****
		p	0.899	0.899	**0.007**	0.114	**0.005**	**0.001**	**0.001**	**0.003**
	HAM-A	r	-0.111	0.111	**-0.343****	0.261	**-0.566****	**0.372****	**0.295***	**0.284***
		p	0.417	0.417	**0.010**	0.052	**0.001**	**0.005**	**0.027**	**0.034**
	BMI	r	-0.063	0.063	-0.013	0.098	-0.009	0.127	0.111	0.111
		p	0.647	0.647	0.924	0.471	0.961	0.350	0.417	0.415
Obesity	**HAM-D**	r	-0.094	0.094	-0.060	0.029	0.140	**0.416****	**0.402****	**0.416****
		p	0.474	0.474	0.651	0.823	0.416	**0.001**	**0.001**	**0.001**
	HAM-A	r	-0.035	0.035	-0.092	-0.010	0.116	**0.287***	**0.334****	**0.340****
		p	0.791	0.791	0.485	0.942	0.502	**0.026**	**0.009**	**0.008**
	BMI	r	-0.190	0.190	-0.126	0.134	-0.185	0.139	0.150	0.111
		p	0.146	0.146	0.339	0.309	0.279	0.290	0.254	0.399
Control	**HAM-D**	r	-0.026	0.014	0.150	-0.059	0.114	0.041	0.126	0.114
		p	0.852	0.923	0.282	0.674	0.520	0.771	0.369	0.418
	HAM-A	r	-0.187	0.200	0.245	0.107	0.011	0.158	0.134	0.128
		p	0.180	0.151	0.077	0.448	0.952	0.258	0.339	0.360
	BMI	r	**-0.340***	**0.329***	0.206	0.255	-0.216	**0.559****	**0.592****	**0.495****
		p	**0.013**	**0.016**	0.139	0.065	0.221	**<0.001**	**<0.001**	**<0.001**

Spearman Correlation analysis. BMI: Body Mass Index, HAM-D: The Hamilton Rating Scale for Depression, HAM-A: Hamilton Anxiety Rating Scale, Stroop Part D: Dots, Stroop Part W: Neutral Words, Stroop Part C: Color Words

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