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Metabolic Effects of Antidepressant Treatment

Antidepresan Tedavinin Metabolik Etkileri

Özlem OLGUNER EKER[1], Saliha ÖZSOY[2], Baki EKER[3], Hatice DOĞAN[4]

[1]Department of Psychiatry, Kayseri Training and Research Hospital, Kayseri, Turkey
[2]Department of Psychiatry, Erciyes University School of Medicine, Kayseri, Turkey
[3]Department of Internal Medicine, Kayseri Training and Research Hospital, Kayseri, Turkey
[4]Department of Child and Adolescent Psychiatry, Kayseri Training and Research Hospital, Kayseri, Turkey

ABSTRACT

Introduction: This study aimed to investigate body measurements, glucose–insulin metabolism, and lipid profile in patients with anxiety and depressive symptoms and also the effects of antidepressant drugs on these metabolic parameters.

Methods: The study included 40 outpatients and 32 healthy controls. The patients received antidepressant treatment (sertraline, escitalopram, fluoxetine, and venlafaxine) for 8 weeks. Body measurements were performed, and lipid, fasting blood glucose, and insulin levels were measured before and after treatment in patients and once in healthy controls. Insulin resistance was evaluated using the homeostasis model assessment (HOMA) index.

Results: Body mass index was higher in patients than in healthy controls, and there was no change in patients after treatment. In patients, high-density lipoprotein (HDL) cholesterol levels increased owing to the antidepressant treatment. Insulin level and HOMA index had a tendency to decrease with the treatment in patients and were similar to those of healthy controls before the treatment; however, they became lower than those of healthy controls after the treatment. There was an increase in waist circumference and total and HDL cholesterol levels, whereas there was a decrease in fasting blood glucose levels with treatment in patients using escitalopram. There was no change in body measurements and biochemical and hormone values in patients using fluoxetine, sertraline, and venlafaxine. There was an increase in weight, body mass index, and waist circumference after treatment in patients with depression; however, there was no change in patients with anxiety.

Conclusion: In patients with psychiatric disorders having anxiety and depressive symptoms, metabolic changes independent of drugs and the metabolic effects of drugs are present.

Keywords: Antidepressant, lipid, insulin, metabolic effect

ÖZ

Amaç: Bu çalışmada anksiyete ve depresif belirtileri olan hastalarda vücut ölçümleri, glukoz-insülin mekanizması ve lipid profilinin araştırılması ve antidepresanların bu metabolik parametreler üzerine etkisinin araştırılması planlanmıştır.

Yöntem: Çalışmaya 40 ayaktan hasta ve 32 sağlıklı kontrol dâhil edilmiştir. Hastalar 8 hafta boyunca antidepresan tedavi (sertralin, essitalopram, fluoksetin ve venlafaksin) almıştır. Hastalarda tedavi öncesi ve sonrası, kontrollerde bir kez olmak üzere vücut ölçümleri yapılmış ve lipid, açlık kan glukozu ve insülin düzeyleri ölçülmüştür. İnsülin direnci, Homeostasis Model Assessment (HOMA) indeksi ile değerlendirilmiştir.

Bulgular: Hastaların beden kitle indeksi yüksek bulunmuştur, ancak tedavi ile değişim olmamıştır. Hastalarda yüksek dansiteli lipoprotein (HDL) kolesterol düzeyleri antidepresan tedaviyle yükselmiştir. İnsülin düzeyi ve HOMA indeksi, tedaviyle düşme eğiliminde olup, tedavi öncesi kontrollerinkinden farksız iken tedavi sonrası kontrollerinkinden düşük hale gelmiştir. Essitalopram kullanan hastalarda bel çevresi, total ve HDL kolesterol düzeylerinde yükselme, açlık kan şekerinde ise tedaviyle düşme görülmüştür. Fluoksetin, sertralin ve venlafaksin kullanan hastalarda vücut ölçümlerinde, biyokimyasal ve hormonal değerlerde değişim olmamıştır. Depresif hastalarda tedavi ile ağırlık, beden kitle indeksi ve bel çevresi ölçümlerinde yükselme olmuştur. Anksiyeteli hastalarda ise değişim olmamıştır.

Sonuç: Anksiyete ve depresif belirtilerle giden psikiyatrik hastalıklarda hem ilaçtan bağımsız metabolik değişiklikler hem de antidepresan ilaçların metabolik etkileri olmaktadır.

Anahtar kelimeler: Antidepresan, lipid, insülin, metabolik etki

INTRODUCTION

Mortality and morbidity are relatively high among patients with severe psychiatric disorders such as schizophrenia, bipolar disorder, and depression compared with those among the general population (1). It is known that patients with severe psychiatric disorders have a shorter life expectancy (2). This decreased life expectancy results from an increased risk for suicide and also medical disorders such as cardiovascular diseases (3). The cardiovascular risk is associated with cardiometabolic risk factors such as diabetes mellitus, smoking, dyslipidemia, and obesity (4). Genetic, lifestyle-related factors, limited access to good quality physical care, the disease itself, and psychopharmacotherapy play a role in the increased risk for cardiovascular diseases (1). Although modifiable cardiometabolic risk factors such as smoking, hyperglycemia, hypertension, dyslipidemia, and obesity are frequently observed in patients with severe psychiatric disorders, they are not sufficiently recognized or are overlooked in these patients (5).

Correspondence Address / Yazışma Adresi: Saliha Özsoy, Erciyes Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Kayseri, Türkiye
E-mail / E-posta: sozsoy@erciyes.edu.tr

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Obesity that results from reduced activity and irregular nourishment is one of the most important risk factors in psychiatric patients. Obesity is more frequently observed among psychiatric patients than among the general population (6). There are many reasons for increased obesity in patients with severe psychiatric disorders (7). Lifestyle alterations related to the psychiatric disorder can cause increased food intake and decreased energy expenditure, thus leading to increased fat accumulation (8). In addition, drugs used for treating psychiatric disorders may also play a role in the etiology of obesity in such patients (9). It is known that psychotropic agents, primarily antipsychotics and mood stabilizers, lead to weight gain. Furthermore, weight gain is a serious problem that can compromise adherence to psychotropic drug regimens and lead to symptomatic relapse and medical comorbidity. In this context, antidepressants have attracted lesser attention than anti-psychotic agents and mood stabilizers. However, if there is a higher risk for antidepressant-related weight gain, it is more important because these drugs are more commonly used. There are a few studies regarding antidepressant-related weight change. It was reported that the likelihood and amount of weight gain may vary in tricyclic antidepressants (TCAs), although TCAs, as a class, are considered to generally result in weight gain through anticholinergic activity (10). In contrast to TCAs, it is proposed that selective serotonin reuptake inhibitors (SSRIs) lead to weight loss rather than weight gain and that these agents decrease carbohydrate intake because they increase serotonin levels (11). Although it was reported that there was initially minimal weight loss and lack of appetite, there was weight gain after completing 1 year of SSRI treatment (12). It is also suggested that each SSRI has a differential effect on weight gain. Despite contradictory results regarding SSRIs, fluoxetine is associated with weight loss, while there is no change or increase in body weight with other SSRIs (13).

Diabetes mellitus, insulin resistance (IR), and hyperglycemia are the most commonly observed metabolic risk factors in the psychiatric population. IR is determined using the homeostasis model assessment of IR (HOMA-IR) index that was first described by Mathews et al. (14). In this method, HOMA-IR index is calculated by using fasting plasma glucose and insulin levels. There is evidence suggesting that the psychiatric disorder itself and/or psychotropic drug use have some effects on the glucose–insulin system. There is a growing body of evidence indicating a positive correlation among depression, diabetes mellitus, and IR (15,16). Moreover, it was shown that chronic stress results in decreased insulin sensitivity without causing weight gain (17). The mechanism that associates IR with depression is unclear. However, it has been suggested that the association is multifactorial (18). It is considered that impaired hypothalamic-pituitary-adrenal (HPA) axis may have a role in the development of IR in patients with major depressive disorder (19). It has also been proposed that at the behavioral level, symptoms such as altered appetite and sleep and reduced activity may cause impaired glucose metabolism whereas at the molecular level, neuroendocrine and inflammatory responses can cause the development of diabetes mellitus along with depression (20,21). However, there are studies suggesting that IR is not associated with depression; it is even protective against depression (22,23).

There are contradictory findings in the studies regarding the effects of antidepressants on insulin sensitivity and glucose homeostasis. In recent years, large epidemiological studies have shown indirect evidence suggesting that antidepressant use increases the risk for diabetes mellitus (24,25). One case–control study revealed that SSRI use increased the risk for the development of type 2 diabetes mellitus (26). A similar effect was observed with serotonin noradrenaline reuptake inhibitor (SNRI) treatment. There are studies that show no change in insulin level and HOMA index.

Dyslipidemia is another risk factor that contributes to mortality and morbidity in psychiatric patients. Conflicting results are found in studies regarding depressive symptoms and lipid profile. Associations between depressive symptoms and low high-density lipoprotein (HDL) levels or elevated triglyceride levels were shown in some studies (31,32,33). Significant associations were found among SSRI use and low HDL, increased total cholesterol level, high triglyceride level, and increased risk for diabetes (34). An increase was demonstrated in total cholesterol level after SSRI treatment (35,36). In some studies, HDL levels were significantly lower in patients with major depressive disorder than in healthy controls, and serum total cholesterol levels were elevated in patients after treatment (32,37). No significant association was found between antidepressant therapy and HDL, total cholesterol, and triglyceride levels in other studies (16,38).

In the light of these data, we planned to investigate obesity, glucose, and lipid metabolism in patients with depression and anxiety symptoms. In addition, we aimed to investigate whether commonly used antidepressant agents, SSRIs and SNRIs, cause weight gain and the effects of these antidepressants on the lipid profile, glucose–insulin system, and body measurements such as waist circumference, fat ratio, and metabolism rate.

METHODS

Subjects

The study included 32 healthy controls and 40 outpatients aged 20–49 years (5 men and 35 women) who presented with depression and anxiety symptoms to the psychiatry outpatient clinic and who were treated with antidepressants. All patients were assessed via a clinical interview. The following disorders were diagnosed in the patients: major depressive disorder (n=8), generalized anxiety disorder (n=8), and adjustment disorder (n=24) based on the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (39).

Patients with metabolic and endocrine disorders (e.g., hyperlipidemia, diabetes mellitus, and thyroid disease), those receiving therapies for these disorders (e.g., anti-diabetic, anti-hyperlipidemic, and hormone therapy), those with psychotic symptoms and using anti-psychotic agents, those with bipolar affective disorder, those receiving a mood stabilizer, those needing to use additional psychotropic agents, those who had used a psychotropic agent within the previous 6 months, those with substance or alcohol abuse, those with an eating disorder, and those on a diet were excluded.

Thirty-two (5 men and 27 women) healthy volunteers with no psychiatric, endocrine, or metabolic disease were included as controls.

The patients and healthy controls were selected after physical and psychiatric examinations, routine biochemical tests, and complete blood count and thyroid function tests.

Patients meeting the inclusion criteria gave written informed consent before participation. The study was approved by the Local Ethics Committee (approval#2012/402).

Procedure

All patients were assessed via a clinical interview and psychometric tests before initiating treatment. Body weight measurements were performed, and blood samples were drawn for biochemical and hormone tests at baseline. Antidepressant treatments were then initiated. Patients were randomly assigned to the antidepressant groups. Antidepressants that are commonly used for the outpatient population with psychiatric disorders

were selected. The following drugs were prescribed to the patients: 50 mg daily sertraline in nine patients, 10 mg daily escitalopram in nine, 20 mg daily fluoxetine in seven, and 75 mg daily venlafaxine in seven. Half of the doses were initiated and titrated to mentioned doses within 1 week. Four weeks after initiating treatment, the dose of venlafaxine was increased to 150 mg daily in three patients and that of escitalopram was increased to 20 mg daily in two patients who were non-responsive to previous doses. Measurements were repeated 8 weeks after initiating treatment. We were unable to obtain posttreatment data for eight patients because of unresponsiveness to treatment, switching drug or adding another drug to the treatment, or withdrawing from the study of their own desire. Measurements were performed once in the healthy controls.

The Hamilton Depression Rating Scale (HDRS) was used to measure the severity of depression (40). The Hamilton Anxiety Rating Scale (HARS) was used for measuring the severity of anxiety symptoms (41).

Waist circumference was measured at the first margin level of the iliac crest after normal breathing in all patients and healthy controls. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

In all patients and healthy controls, blood samples were drawn at 08:00-09.00 AM after 12 hours of fasting for measuring fasting blood glucose, triglyceride, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and insulin levels. Biochemical analyses were performed on the same day using the Synchron LX system (Beckman Coulter; Fullerton, CA, USA). For hormone assays, blood samples were centrifuged within 30 min after sampling, and the serum samples were stored at −70°C until assays. The serum insulin level was measured using an immunoradiometric assay kit (DIAsource ImmunoAssays S.A.; Louvain-la-Neuve, Belgium). The sensitivity limit was 1μIU/mL, whereas the intra- and interassay coefficients of variance were 2.1% at 6.6 μIU/mL and 6.5% at 14.4 μIU/mL concentrations, respectively. The HOMA index was calculated using the following formula:

HOMA-IR index=fasting insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405

Statistical Analysis

Data distribution was tested using the Shapiro–Wilk test. To compare demographic, clinical, biochemical, and hormone data between the patient and control groups, the independent samples t-test was used for data with normal distribution, whereas the Mann–Whitney U test was used for data with skewed distribution. The hormone values of the patients and healthy controls were also compared with the multivariate analysis of covariance (MANCOVA) test by considering BMI as the covariate to control the contributing effect of BMI. The chi-square test was used to compare categorical values such as the women/men ratio and smoker/non-smoker ratio of the patients and healthy controls. To compare pre- and posttreatment data, paired samples t-test was used for data with normal distribution, whereas the Wilcoxon test was used for data with skewed distribution. Because of the limited number of subjects in the subgroups, the non-parametric Wilcoxon test was used to compare changes with treatment in different drug and diagnosis groups. The Spearman correlation test was used to evaluate associations among demographic, clinical, biochemical, and hormone data. In the tables, data with normal distribution are expressed as mean±standard deviation, whereas those with skewed distribution are expressed as median (interquartile range).

RESULTS

There were no significant differences between the patient and control groups regarding age ($Z=0.102$, $p=0.919$), gender ($X^2=0.145$ $p=0.703$), smoker rate ($X^2=2.037$ $p=0.154$), duration of smoking ($Z=0.584$, $p=0.559$),

Table 1. Demographic and clinical characteristics of patients and healthy controls

	Patient		Healthy controls (n=32) median (interquartile range)
	Pretreatment (n=40), median (interquartile range)	Posttreatment (n=32) median (interquartile range)	
Age	31 (15)	-	29.5 (9)
Education (year)	11 (6.75)[a]	-	16 (3.75)
Female/male	35/5	-	27/5
Smoker/non-smoker	12/28	-	5/27
Duration of smoking (year)	9 (15)	-	8 (14)
Number of cigarettes per day	7.5 (15)	-	10 (17.5)
HDRS score	20.5 (8)[b]	11 (7.75)[c]	0 (2)
HARS score	28.5 (17)[d]	11.5 (18.75)[e]	3.5 (2.75)
Total duration of illness (year)	2 (4)	-	-
Duration of last episode (month)	5.5 (11)	-	-
Number of episode*	2 (1)	-	-

HDRS: Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale

*: Periods of disease exacerbation were accepted as episodes for patients with chronic disorders.

[a]: lower than that of healthy controls ($Z=5.912$, $p<0.001$)

[b]: higher than that of healthy controls ($Z=7.307$, $p<0.001$)

[c]: higher than that of healthy controls ($Z=6.302$, $p<0.001$)

[d]: higher than that of healthy controls ($Z=7.266$, $p<0.001$)

[e]: higher than that of healthy controls ($Z=5.895$, $p<0.001$)

and number of cigarettes smoked per day (Z=0.884, p=0.377). Education level was higher in the control group than in the patient group (Z=5.912, p<0.001). Both pre- and posttreatment HDRS and HARS scores were significantly higher in the patient group than in the control group (Z=7.307, p<0.001; Z=7.266, p<0.001; Z=6.302, p<0.001; Z=5.895, p<0.001, respectively). HDRS and HARS scores decreased after antidepressant treatment (Z=4.939, p<0.001; Z=4.680, p<0.001, respectively) (Table 1).

At baseline, body weight and BMI values were higher in the patient group than in the control group. After treatment, body weight and BMI values were higher in the patient group than in the control group. Treatment did not cause a significant change in the body weight or other body measurement values of the patient group (Table 2).

At baseline, there were no significant differences in triglyceride, total cholesterol, and LDL cholesterol levels between the patient and control groups. Non-HDL cholesterol levels were higher and HDL cholesterol levels were lower in the patient group than in the control group. After treatment, triglyceride and HDL cholesterol levels in the patient group were identical to those in the control group, whereas total, non-HDL, and LDL cholesterol levels were higher in the patient group than in the control group (Table 3). When the effect of the antidepressant treatment was considered, it was observed that total cholesterol and HDL levels were elevated after treatment. There was no significant difference in non-HDL levels with treatment (Table 4).

The pretreatment fasting blood glucose levels were higher in the patient group than in the control group, and they were identical to those in the control group after treatment. Although there were no significant differences in baseline insulin levels and HOMA index values between the patient and control groups, these values were lower in the patient group than in the control group after treatment (Table 5). When adjusted hormone values, to control the effect of BMI, were compared, similar results were obtained. Furthermore, insulin levels were lower in the patient group than in the control group, and the HOMA index values tended to be lower in the patient group than in the control group after treatment (Table 5). When hormone values at pre- and posttreatment were compared, insulin levels and HOMA index values tended to decrease but did not reach a statistical significant level (p=0.081 and p=0.059, respectively) (Table 4).

There was no change in body measurement or biochemical values or insulin levels with treatment in patients who received sertraline, fluoxetine, and venlafaxine. It was observed that waist circumference values (Z=1.983, p=0.047) and total (Z=2.194, p=0.028) and HDL cholesterol (Z=2.106, p=0.035) levels increased, whereas fasting blood glucose levels (Z=2.194, p=0.028) decreased with treatment in patients who received escitalopram.

In patients with depression, it was observed that body weight (Z=2.207, p=0.027), BMI (Z=2.207, p= 0.027), and waist circumference (Z=2.264, p=0.024) values increased with treatment. In patients diagnosed as

Table 2. Pre- and posttreatment body measurements in patients and healthy controls

	Patient		Healthy controls (n=32)
	Pretreatment (n=40)	Posttreatment (n=32)	
Body weight (kg)	67.8 (14)[a]	69.15 (13)[b]	60.6 (12.5)
Body mass index (kg/m^2)	26.7 (6.98)[c]	26.85 (6.15)[d]	23 (3.52)
Height (m)	1.60 (0.07)	-	1.59 (0.1)
Waist circumference (cm)	92.35±11.59	92.87±10.93	91.31±9.29

[a]: higher than that of healthy controls (Z=2.148, p=0.032)
[b]: higher than that of healthy controls (Z=2.437, p=0.015)
[c]: higher than that of healthy controls (Z=2.431, p=0.015)
[d]: higher than that of healthy controls (Z=2.652, p=0.008)

Table 3. Comparison of pre- and posttreatment lipid profiles of patients and healthy controls

	Patient		Healthy controls (n=32)	Comparison	
	Pretreatment (n=40)	Posttreatment (n=32)		Pretreatment controls	Posttreatment controls
Triglyceride (mg/dL)	93.5 (68.75)	88 (58)	79.5 (46.5)	Z=1.332 p=0.183	Z=1.558 p=0.119
Cholesterol (mg/dL)	180.27±39.35	193.06±41.87**	168.81±28.23	t=1.386 p=0.170	t=2.716 p=0.009
LDL cholesterol (mg/dL)	105.5 (45.45)	111.8 (39.05)**	92.8 (31.55)	Z=1.768 p=0.077	Z=2.592 p=0.010
HDL cholesterol (mg/dL)	46.62±9.98*	49.97±10.45	51.62±10.30	t=2.083 p=0.041	t=0.639 p=0.525
Non-HDL cholesterol (mg/dL)	128 (49)**	129.5 (42)**	111 (41.25)	Z=2.046 p=0.041	Z=2.868 p=0.004

HDL: high-density lipoprotein; LDL: low-density lipoprotein
*: lower than that of healthy controls
**: higher than that of healthy controls

Table 4. Comparison of pre- and posttreatment biochemical values of patients

	Pretreatment (n=32)	Posttreatment (n=32)	Comparison
Triglyceride (mg/dL)	96 (74.75)	88 (58)	Z=0.298 p=0.765
Total cholesterol (mg/dL)	183.66±41.64	193.06±41.87**	t=2.431 p=0.021
LDL (mg/dL)	110.5 (46.24)	111.8 (39.05)	Z=1.739 p=0.082
HDL (mg/dL)	47.12±10.12	49.97±10.45**	t=2.683 p=0.012
Non-HDL cholesterol (mg/dL)	132 (51.75)	129.5 (42)	Z=1.794 p=0.073
Fasting blood glucose (mg/dL)	89.34±6.64	87.31±9.44	t=1.557 p=0.130
Insulin (µIU/mL)	14.9 (8.12)	12.25 (7.22)	Z=1.744 p=0.081
HOMA index	3.29 (1.73)	2.82 (1.76)	Z=1.889 p=0.059

HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA: homeostasis model assessment
**: higher than pretreatment values

Table 5. Comparison of pre- and posttreatment glucose–insulin levels of patients and healthy controls

	Patient		Healthy controls (n=32)	Comparison	
	Pretreatment (n=40)	Posttreatment (n=32)		Pretreatment controls	Posttreatment controls
Fasting blood glucose (adjusted mean±SD)	88.97±7.61**	87.31±9.44	83.75±9.30	t=2.622 p=0.011	t=1.521 p=0.133
Insulin [median (interquartile range)]	17.3 (5.3)	12.25 (7.23)*	18.1(13.2)	Z=0.595 p=0.552	Z=2.142 p=0.032
HOMA index [median (interquartile range)]	3.48 (1.52)	2.82 (1.77)*	3.52 (2.61)	Z=0.011 p=0.991	Z=2.001 p=0.045
Insulin (adjusted mean±SD)	17.13±1.68	13.43±2.15*	19.64±1.88	F=0.952 p=0.333	F=4.189 p=0.045
HOMA index (adjusted mean±SD)	3.80±0.37	2.91±0.45	4.04±0.42	F=0.177 p=0.675	F=3.135 p=0.082

SD: standard deviation; IR: interquartile range
*: lower than that of healthy controls
**: higher than that of healthy controls

having adjustment disorder with depressed mood, it was observed that total cholesterol (Z=2.845, p=0.004) and LDL cholesterol (Z=2.845, p=0.004) levels increased, whereas HDL cholesterol levels (Z=2.316, p=0.021) decreased after treatment. In patients with adjustment disorder with anxious mood and generalized anxiety disorder, there was no change in body measurement, biochemical, and hormone values.

It was found that the baseline severity of depression and anxiety were negatively correlated with total cholesterol levels (r=−0.325*, p=0.041 and r=−0.343*, p=0.030, respectively) and LDL cholesterol levels (r=−0.325*, p=0.029 and r=−0.343*, p=0.030; respectively). There were positive correlations between baseline severity of depression and total duration of illness (r=0.325*, p=0.041) and negative correlation between baseline severity of anxiety and duration of last episode (r=−0.483**, p=0.002). No correlation was found among total duration of illness, duration of last episode, number of episodes, and body measurement and biochemical values in patient group before treatment. There was a negative correlation between the HDRS score and waist circumference values (r=−0.392*, p=0.026) and fasting glucose levels (r=−0.377*, p=0.033) in the patient group after treatment. It was found that there was a positive correlation among HDRS score and body weight (r=0.370*, p=0.037), BMI (r=0.392*, p=0.027), and waist circumference values (r=0.458**, p=0.008) in the control group.

DISCUSSION

Effects of Disease and Antidepressants on Body Measurement Values

This study aimed to investigate the effects of common psychiatric disorders, such as depression and anxiety, and antidepressants that are frequ-

ently used to treat these disorders on metabolic parameters. When the findings of body measurements of the patients were reviewed, body weight and BMI values were found to be higher in the patient group than in the control group, both at baseline and after treatment. In other words, it appears that patients gained weight before drug treatment. Although this may be related to the selection of patients and healthy controls, the finding that patients had higher body weight than randomly selected healthy controls remains noteworthy. It is known that patients with severe psychiatric disorders such as schizophrenia and bipolar affective disorder gain weight, and this is a risk factor that affects mortality and morbidity (1). The results of our study emphasize that weight gain independent of treatment occurs in anxiety and depressive disorders. There may be several reasons for greater body weight in these patients. Lifestyle modifications owing to the disease and disease symptoms such as altered appetite, sleep, and physical activity may play a role in weight gain (8). Increased appetite and sleep with reduced activity appear to be related to weight gain in patients with depressive disorders. There are positive correlations between the severity of depressive symptoms and variables such as body weight, BMI, and waist circumference values even in healthy controls. In other words, depressive symptoms can be related to weight gain in an individual without depression at the diagnostic level. Previous studies also demonstrated that increased depressive symptoms were associated with weight gain in the general population (42). Depression was associated with a particular increase in waist circumference values, possibly leading to the development of metabolic syndrome and diabetes mellitus (43).

One of the major results of this study is that there is no change in body weight, BMI, and waist circumference values in patients who received antidepressant treatment after 8 weeks. In summary, antidepressants used in this study appear to have had no significant effect on body measurements during the 8 weeks of treatment. However, waist circumference values increased in patients who received escitalopram compared with those who received other drugs. Although the number of studies investigating the effects of antidepressants on body measurements is limited, these studies indicate that long-term use of antidepressants, even SSRIs, causes increases in body measurements such as weight, waist circumference, and body fat mass (16,36,44). In this study, the lack of marked effect on body measurements could be related to the short duration of treatment. However, increased waist circumference values in the escitalopram group may support the hypothesis of the increasing effect of antidepressants on body measurements. In the other antidepressant groups, there was also a numeric increase in waist circumference values, which did not reach statistical significance. Given that increased waist circumference is more important than weight gain as a risk factor, it would be reasonable to suggest that antidepressants can contribute to an increased metabolic risk. However, different antidepressants may have different effects on body measurements.

The study included patients with depression, generalized anxiety disorder, adjustment disorder with depressed mood, and adjustment disorder with anxious mood. Among these, body weight, BMI, and waist circumference values increased with treatment in patients with depression. In other words, the effects of antidepressant treatment on important metabolic parameters appear to be marked in depressive patients. This could also be interpreted as depression that causes more impairment in metabolic parameters compared with anxiety. Previous studies reported that depression, but not anxiety, is related to metabolic syndrome (44). Also, in our study, metabolic alterations appear to be related to depression.

Effects of Antidepressants on Lipid Profile

In our study, total cholesterol and HDL cholesterol levels were elevated with antidepressant treatment. Some previous studies reported that cholesterol levels increased, whereas HDL cholesterol levels decreased after antidepressant treatment (34,36). These findings emphasize that antidepressants worsen metabolic status by adversely affecting the lipid profile. Similarly, an increase was detected in total cholesterol levels in our study. Elevated HDL levels in our study were inconsistent with the hypothesis that suggested a negative effect. However, it is observed that elevations in total cholesterol levels resulted from elevated HDL levels when the comparison was repeated after calculating non-HDL cholesterol levels. In other words, only HDL levels appeared to increase with antidepressant treatment. In conclusion, antidepressants used in this study showed a positive effect on the lipid profile during the 8 weeks of treatment. Although it is possible to make such an interpretation, in general, the heterogeneity of diagnoses and drugs should be considered. In the homogenous group of a larger study, it was found that SSRIs have different effects on the lipid profile. In the study by Beyazyuz et al. (45), total cholesterol and triglyceride levels were elevated by paroxetine but were reduced by fluoxetine. Similar to our study results, Yosmaoglu et al. (36) found that there was an increase in total cholesterol level and a borderline elevation in HDL levels in their study, in which several antidepressants were used. In our study, it was observed that total cholesterol and HDL levels increased in the escitalopram group, whereas no alteration was observed in the other drug groups. However, the limited number of patients in these subgroups makes it difficult to draw conclusions regarding the effects of different SSRIs; however, it should be noted that different SSRIs have different effects on the lipid profile.

Glucose–Insulin Metabolism

At baseline, insulin levels and HOMA index values in the patient group were similar to those in the control group, whereas after treatment, those values became lower than those in the control group, with a tendency to decrease with treatment. At baseline, fasting blood glucose level was higher in the patient group than in the control group, whereas after treatment, it decreased to a level similar to that in the control group. Higher insulin levels and HOMA-IR index values are associated with an increased risk for diabetes mellitus (46). Thus, decreased blood glucose and insulin levels and HOMA-IR index values after 8 weeks of antidepressant treatment could be interpreted as SSRI use-decreasing diabetes risk. Although alterations during this period did not reach clinical significance, these findings may emphasize the altered risk in the long term.

There are contradictory results in studies that investigated the effects of antidepressants on insulin sensitivity and glucose homeostasis. Some studies suggest that antidepressant use increases the risk for development of diabetes mellitus (24,26), whereas some other studies suggest positive (28,30) or no effects (27). Our results indicate that 8 weeks of SSRI treatment may have a positive effect on glucose–insulin metabolism. Studies emphasizing the increased risk for diabetes with antidepressant use generally involve those demonstrating an association between diabetes and antidepressant use in large populations (24,25). However, majority of studies assessing glucose metabolism before and after antidepressant use demonstrated positive or no effects (27,28). There is a need for long-term studies using this methodology.

In summary, depression is associated with impaired glucose metabolism, and the effects of antidepressant use on glucose metabolism appear to be unclear. In our study, we failed to demonstrate this association as it did not comprise depressive patients alone. However, our results present evi-

dence that suggest that short-term antidepressant use has positive effects on glucose metabolism.

Limitations

Although the number of participants was sufficient in the patient and control groups, the numbers were decreased when the groups were stratified into subgroups according to drugs and diagnoses. In addition, the number of male participants was lesser than that of females, although the female/male ratios were similar in the patient and control groups. This makes it difficult to analyze with respect to sex. However, we cannot generalize the results because of the small number of male patients. There was a significant difference in BMI values between the patient and control groups. However, BMI values were used as covariates in the statistical analyses of hormone values to eliminate the impact of this difference. Moreover, the study period of 8 weeks might have been insufficient to allow the effects on body measurements and metabolic parameters to be revealed. However, our study period is longer than that of similar studies and allowed us to detect some changes. Nevertheless, it would be interesting to determine how body measurements change in these patients in a longer follow-up, such as 6 or 12 months. We previously reported serum neuropeptide Y levels in these patients and alteration in neuropeptide Y levels during 6 months of antidepressant treatment in some of them (47).

CONCLUSION

In conclusion, this study shows that there is weight gain independent of the treatment in disorders that present with anxiety and depressive symptoms. Antidepressants used in this study appeared to have had no significant effect on body measurements during 8 weeks of treatment. Decreased insulin level and HOMA index value and increased HDL levels with antidepressant treatment demonstrated the positive effect of antidepressants on the glucose–insulin system and lipid profile. These positive alterations may also be a result of improvement in the depressive symptoms. Improvement of depressive symptoms might have caused positive changes in lifestyle such as regular feeding and physical activity. Consequently, both metabolic alterations independent of drug use and metabolic effects of antidepressant drugs occur in diseases that present with anxiety and depressive symptoms. There is a need for studies with larger sample size and long-term follow-up.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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