

Evaluation of the Levels of Adiponectin, Ghrelin, and Resistin in Alcohol Dependent Male Patients

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ÖZET:

Alkol bağımlısı erkek hastalarda grelin, resistin düzeylerinin değerlendirilmesi

Amaç: Alkol bağımlılığının etiolojisine ilişkin pek çok kuram olduğu bilinmesine rağmen, günümüzde üzerinde en çok fikir birliğine varılan yaklaşım; alkol bağımlılığını, etiolojisinde biyolojik, psikolojik ve sosyal pek çok etkeni içeren bir bozukluk olarak kabul eden çok boyutlu yaklaşımdır. Son yıllarda özellikle biyolojik faktörler üzerinde durulmakta ve çeşitli biyolojik parametreler üzerinde araştırmalar yapılmaktadır. Özellikle alkol kullanan bireylerin tümünde alkol bağımlılığının gelişmemesi, klinik seyrinin farklılık göstermesi, düzelleme ve yineleme özelliklerinin kestirilememesi nedeniyle bağımlılık için risk etkenlerinin, olası biyolojik parametrelerin araştırılmasına ihtiyaç duyulmaktadır. Bunun için vücutta çeşitli rolleri olan hormonlar araştırma konusu olmuştur. Besin alımını etkileyen hormonların alkol alımını da etkileyebileceği düşünülebilir. Bu çalışmada besin alımını etkileyen hormonlar olan adiponektin, grelin ve resistinin alkol alımını üzerinde etkisinin olup olmadığının ve alkol bağımlılığı için belirteç olabileceği hipotezinin araştırılması amaçlanmıştır.

Yöntem: Bu çalışmaya Ankara Numune Eğitim ve Araştırma Hastanesi AMATEM kliniğinde yatarak tedavi gören, Ruhsal Bozuklukların Tanımlanması ve Sınıflandırılması II Kitabı-Dördüncü Baskı (DSM-IV) ölçütlerine göre yapılan klinik değerlendirme sonucu alkol bağımlılığı tanısı alan 107 erkek hasta dâhil edildi. Hastaneye yatışlarının ilk günü (alkol alımını bıraktıkları gün, 0. gün) ve 7. gün sabah saat 08:00'de aç olarak kanları alındı ve adiponektin, grelin ve resistin düzeyleri ölçüldü. Kontrol grubu için en az on gündür alkol içmeyen, DSM-IV ölçütlerine göre alkol bağımlılığı veya kötüye kullanımı tanı ölçütlerini karşılamayan, hasta grubu ile uyumlu olarak 83 gönüllü kişi seçildi. Kontrol grubundan adiponektin, grelin ve resistin düzeyleri için bir kez kan alındı.

Bulgular: Alkol bağımlılığı olan hasta grubu ile kontrol grubu arasında adiponektin, grelin ve resistin düzeylerinde istatistiksel olarak anlamlı fark bulundu. Adiponektin ve grelin düzeyleri birinci gün kontrol grubuna göre anlamlı olarak yüksek iken 7. günde anlamlı olarak düşüş gösterdi. Resistin düzeyleri ise başlangıçta kontrol grubuna kıyasla anlamlı olarak yüksek iken 7. Günde anlamlı olarak yükseklik devam etti.

Sonuçlar: Her üç belirtecin alkol bağımlılarında alkolü bırakmayı takiben günler içinde değişim göstermiş olması, konuda daha fazla çalışma yapılmasına gerek olduğunu ve daha uzun süreli aykılık dönemlerinin değerlendirilmesinin faydalı olabileceğini düşündürmektedir. Bu çalışma, alkol bağımlılarında adiponektin, grelin ve resistin düzeylerinin alkol kullanımı ile ilişkili biyolojik bir belirleyici olabileceğini göstermiştir. Ancak bunun için ileri araştırmalara ihtiyaç vardır. Çalışmamız konu ile ilgili ileri araştırmalara ışık tutabilir.

Anahtar sözcükler: Alkol bağımlılığı, adiponektin, grelin, resistin

Klinik Psikofarmakoloji Bülteni 2012;22(3):216-24

ABSTRACT:

Evaluation of the levels of adiponectin, ghrelin, and resistin in alcohol dependent male patients

Objective: There are numerous theories about the etiology of alcohol dependence, at the present time. The most widely accepted hypothesis is a multidimensional approach which includes biological, psychological, and sociological factors playing roles in the etiology and deeming alcohol dependence a disorder. In recent years, the biological factors have been the focus of investigation and various biological parameters have been studied. Since alcohol dependence does not develop in all individuals consuming alcohol, its clinical course varies, and the features of recovery and recurrence of alcohol dependence cannot be predicted; therefore, it is important to investigate the risk factors and possible biological parameters of dependence (5,6). A number of hormones that play various roles in the body have become the subject of research. Hormones affecting food intake may have an effect on alcohol consumption. The purpose of this study was to investigate whether the hormones (adiponectin, ghrelin, and resistin) affecting food intake have an effect on alcohol consumption and the hypothesis that they could be indicators for alcohol dependence.

Methods: One hundred and seven male patients were included in the study, who were hospitalized at the AMATEM Unit of Ankara Numune Training and Research Hospital for treatment. They were clinically evaluated and diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria. Fasting blood samples were collected at 08:00 AM on the first day of hospitalization, which was also the day the patients gave up drinking (day 0), and then on the following 7th day to measure adiponectin, ghrelin, and resistin levels. Eighty-three healthy male volunteers, who had not consumed any alcohol for at least ten days, did not meet diagnostic criteria for alcohol dependence or abuse based on the DSM-IV criteria, and were compatible with patient group, were included in this study. Blood samples were taken from the control group once to determine levels of adiponectin, ghrelin, and resistin.

Results: There was a statistically significant difference between the alcohol dependent patient group and the healthy control group in terms of adiponectin, ghrelin, and resistin levels. On the first day, the adiponectin and ghrelin levels of the patient group were significantly higher compared to the control group and significantly lower on the seventh day. Resistin levels were significantly higher compared to the control group on the first day and continued to increase significantly on the seventh day.

Conclusions: Since all three parameters changed throughout the days after quitting alcohol in the alcohol dependent patients, there is a need for further studies to be conducted on this subject. The evaluation of more prolonged sobriety days may also be useful. This study showed that adiponectin, ghrelin, and resistin levels could be biological indicators for alcohol dependence. However, in order to prove this hypothesis, further studies are required. This study points the way for future studies to be conducted on the subject.

Key words: Alcohol dependence, adiponectin, ghrelin, resistin

Bulletin of Clinical Psychopharmacology 2012;22(3):216-24

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Gönderme tarihi / Date of submission: 10 Aralık 2011 / December 10, 2011

Kabul tarihi / Date of acceptance: 31 Temmuz 2012 / July 31, 2012

Bağıntı beyanı:

N.A.K., N.D., B.Y.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:

N.A.K., N.D., B.Y.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Alcohol dependence could be defined as a condition such that, when the individual drinks alcohol and cannot withstand the desire to continue drinking alcohol so frequently, it destroys her/his physical and mental health, and familial, social, and professional harmony (1). While there have been a number of theories regarding the etiology of the alcohol dependence, today's most widely accepted one is the multidimensional approach, which deems alcohol dependence as a disorder and considers that many biological, psychological and social factors play a role in its etiology. In recent years, the biological factors have been emphasized and studies have been conducted on various biological parameters. Due to the fact that alcohol dependence does not develop in all individuals who consume alcohol, its clinical course varies, and its recovery and recurrence properties cannot be predicted. For this reason, it is required to investigate the risk factors and possible biological parameters for dependence (5,6). A number of hormones that play various roles in the body have become the subject of research. Adiponectin, ghrelin, and resistin (an adipocytokine) are thought to play roles in regulating eating behaviors, and are among the parameters that have been investigated in alcohol-dependent patients (10,23).

Adiponectin is synthesized from white adipose tissue and it plays a role in hypothalamic appetite regulation (7). Adiponectin has been frequently studied in glucose metabolism, weight gain, and inflammation in atherogenic processes. In animal studies, adiponectin injection caused weight loss and increased energy consumption without decreasing food intake. Similar to the mechanism of leptin, it is thought to have an effect through the HPA axis. The studies, which accept that it has an effect through the central nervous system, showed that adiponectin crosses the blood-brain barrier (8). Adiponectin receptors have been found in the hypothalamus and they are thought to be in charge of central appetite regulation (8,9). After its effects had been shown in the central nervous system, adiponectin became a subject of alcohol craving studies as an indicator like leptin and ghrelin. In a study that was published in 2009, the adiponectin level was examined in alcohol addicts during the active addiction period and it was found to be significantly higher compared to the healthy control group (10).

Ghrelin was defined as the endogenous ligand of the Growth Hormone Secretagogue Receptor (GHS-R) in the

rat stomach for the first time in 1999. In recent times, the role of ghrelin in alcohol dependence has been discussed and both its increasing and decreasing levels have been defined (11,12). Some studies revealed that it was also associated with alcohol craving (12,13).

Resistin is one of the indicators called adipocytokines. It is synthesized by mononuclear cells and macrophages in white adipose tissue. In a general sense, it is accepted to function in the opposite direction to that of adiponectin. Studies have shown that the resistin gene is expressed in the hypothalamus and pituitary gland (14). In a study conducted in 2004, resistin was indicated to have an effect on dopamine and norepinephrine secretion from the hypothalamus (15). In another study which looked at adiponectin and resistin together based on the effects on the central nervous system, during the active drinking phase and after detoxification phase (day 7), the levels of adiponectin and resistin were found significantly higher compared with healthy control group (10).

Clinical research is needed to determine the possible role of these hormones with studies considering the development, clinical course, and recovery and recurrence properties of alcohol dependence and its treatment.

This study investigated whether the hormones that affect food intake also have an effect on alcohol consumption and dependence. For that purpose, adiponectin, ghrelin and resistin levels in inpatients with alcohol dependence were compared with those of a healthy control group on the first and seventh days of treatment.

MATERIALS AND METHODS

Patient Selection

The sample group of this study consisted of patients, who were hospitalized in the 2nd Psychiatry Unit of the Alcohol and Drug Addiction Treatment Center (AMATEM) service of Ankara Numune Training and Research Hospital (ANEAH). A total of 107 male patients, who were treated between August 2009 - February 2010 and met the inclusion criteria and a control group of 83 healthy people were included in the study. Both written and verbal informed consent was received from all of the participants who were included in the study. The study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital. Each patient included in the study was assessed

using the sociodemographic data form and SCID-1. Their withdrawal levels were determined with the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), which was applied on the day they were hospitalized.

Inclusion Criteria for the Study

- Meeting the criteria of Alcohol dependence diagnosis according to the DSM- IV,
- Being 18 or older and 65 or younger,
- Having the cognitive capacity to comprehend the tests and instructions to be given and being literate,

Inclusion criteria for the control group:

- Being a healthy volunteer participant between the ages of 18 and 65
- Having no psychiatric disorder
- Having no misuse and/or dependence of alcohol or other substances
- Having no known physical illness
- Having the cognitive capacity to read and comprehend the tests and instructions and being literate,
- Having not used alcohol for at least 10 days

Exclusion Criteria for the Study

- Being younger than 18 or older than 65
- Having a diagnoses of comorbid axis I or axis II disorder according to the DSM-IV TR
- Having misuse/ dependence of substances other than alcohol or cigarettes
- Being diagnosed with a somatic disease (Hypertension, Diabetes Mellitus, Romatoid Arthritis)
- Having HPA axis or thyroid disease
- Using a medication that affects metabolism
- Using a chronic medication
- Having an endocrine disease
- Having dementia or other organic mental disorders

Instruments

1. Sociodemographic Data Form

This is a form that has been developed by researchers, consisting of information such as age, gender, marital status, and educational level, which is used for the purpose of evaluating the characteristics of patients.

2. Structured Clinical Interview for DSM-IV Axis Disorders (SCID-I)

This is a structured clinical interview scale that was developed to establish Axis I diagnoses. Structured interviews were developed in an attempt to increase the reliability of the diagnosis by standardizing the assessment process and to check for some unnoticeable symptoms systematically. It is a clinical diagnosis instrument, which was structured by First et al. (16). The adaptation and reliability studies for the Turkish population were conducted by Çorapçıoğlu et al. (17).

3. Clinical Institute Withdrawal Assessment for Alcohol (CIWA-AR)

Developed by Sullivan et al. (18), the Clinical Institute Withdrawal Scale for Alcohol (CIWA-AR) is used in an attempt to determine the severity of the alcohol withdrawal syndrome and the degree of physical addiction. This scale evaluates deprivation symptoms in 10 different areas, such as nausea and vomiting, tremor, perspiration, anxiety, agitation, tactile, auditory and visual disorders, headache, feeling of fullness in the head, orientation, and clouding of consciousness. It is assessed on a total of 67 points (the tenth item between 0-4 points and others between 0-7 points). The scale has been translated into Turkish by Kalyoncu et al. (19) and the Cronbach Alpha internal consistency coefficient was found to be 0.80.

4. Measurement of the Ghrelin Levels

Ghrelin levels were examined by a radio immune assay (RIA) using a 1470 Wizard Gamma Counter.

5. Measurement of the Adiponectin Levels

Adiponectin levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a Sirio enzyme reader.

6. Measurement of the Resistin Levels

Resistin levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a Sirio enzyme reader.

Procedure

At 08:00 in the morning on the first day (the day they quit alcohol, day 0) and the seventh day of hospitalization, fasting blood samples were taken from the patients and ghrelin, adiponectin, and resistin levels were measured. At the same time, the Clinical Institute Withdrawal Scale for Alcohol (CIWA-AR) was administered. The patients were given diazepam of 0-40 mg, according to the severity of their deprivation symptoms. None of the patients developed delirium tremens. Their diazepam doses were decreased and discontinued within one week. During the treatment, all of the inpatients were given vitamin B complex supplements. No other drugs were given to the patients. During the twenty-eight-day abstinence period, the blood/breath alcohol levels of the patients were tested, starting from the day they quit alcohol and throughout their stay in the AMATEM unit. A single blood sample was collected from the control group, in order to measure the adiponectin, ghrelin, and resistin levels.

Statistical Methods

The SPSS 15.0 software package was used to assess the data. In the statistical analysis, the descriptive results of the frequency test were expressed as mean $\pm$ standard deviation (mean $\pm$ SD) for the distribution of sociodemographic features. To compare percentages in patient and control groups, the Chi Square test was used. Since the data did not show a normal distribution, the Mann-Whitney and Wilcoxon tests, which are non-parametric tests, were used and their results were given as the median value (min-max). $P < 0.05$ was accepted as the significance level. The relationships of the patient and control groups were examined in terms of BMI and age and a covariance analysis was performed.

RESULTS

The study and control groups were composed of only male participants. The sample group consisted of a total of 190 people (107 in the patient group and 83 in the control group). The mean age of the alcohol dependent patients who participated in the study was determined to be 44.07 ± 10.00 and it was 34.43 ± 8.80 in the control group. The characteristics such as age, weight, height and body mass index of the patient and control groups were compared. No statistically significant difference was found between the patient and control groups in terms of body mass index. While the age was significantly higher in the patient group, no significant difference found between the weights and heights.

Results Obtained from Evaluation of the Serum Adiponectin Levels

The median value of the adiponectin levels of patients was determined to be 12300 (1600–15000) ng/ml on day 0 and it was 11000 (700–15000) ng/ml on the 7th day. The Wilcoxon test showed a statistically significant difference between adiponectin levels on day 0 and day 7 ($p=0.009$, $p < 0.05$). The values on day 7 were statistically significantly lower compared to the values on the day 0. The relationship of adiponectin values with BMI was assessed with Spearman's correlation analysis. No relationship was determined. Table 1 illustrates the change in the patients' adiponectin levels with respect to days of abstinence.

Results Obtained from Evaluation of the Serum Ghrelin Levels

The median value of the ghrelin levels of patients was determined to be 1000 (530–3200) ng/ml on day 0 and to

Table 1: Comparison of Adiponectin, Ghrelin, and Resistin Levels of the Patient Group on Day 0 and 7

	N	Mean $\pm$ Std. Deviation	Median (Min-Max)	p value
Adiponectin0	107	10771.96 $\pm$ 4152.81	12300(1600-15000)	0.009*
Adiponectin7	107	10218.69 $\pm$ 4253.19	11000(700-15000)	
Ghrelin0	107	1147.89 $\pm$ 477.99	1000(530-3200)	0.023*
Ghrelin7	107	1113.70 $\pm$ 578.77	960(400-4600)	
Resistin0	107	3434.11 $\pm$ 2168.693	2750(560-10000)	0.141
Resistin7	107	4496.96 $\pm$ 2223.867	4000(1100-10000)	

(Wilcoxon test for Ghrelin and Adiponectin ($p < 0.05$). Covariance analysis for Resistin in repeated measures (repeated measures ANCOVA) ($p > 0.05$)

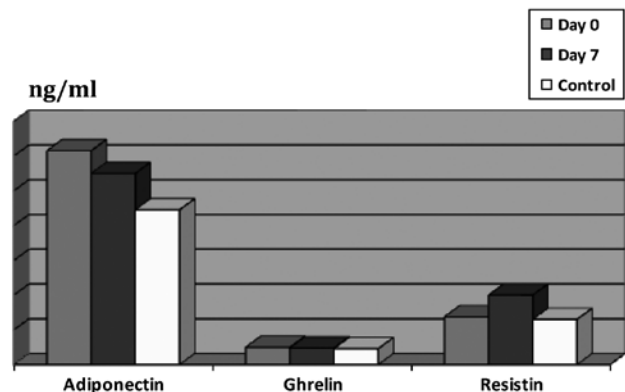
Table 2: Comparison of Adiponectin, Ghrelin, and Resistin Levels of the Patient and Control Groups

status		Patient	control	grp p value	bmi p value	
Adiponectin0	Mean±Std. Error		10780.±2445.43	89328.69±3162.53	p<0.001	0.873
	95% Confidence	Lower Bound	5953.29	83085.26		
	Interval	Upper Bound	15608.71	95572.12		
Ghrelin0	Mean±Std. Error		1146.35±144.24	9028.89±181.01	p<0.001	0.779
	95% Confidence	Lower Bound	861.63	8671.60		
	Interval	Upper Bound	1431.06	9386.19		
Resistin0	Mean±Std. Error		3411.99±769.68	30212.80±1064.22	p<0.001	0.244
	95% Confidence	Lower Bound	1891.94	28111.07		
	Interval	Upper Bound	4932.04	32314.52		
Adiponectin7	Mean±Std. Error		10228.95±2446.39	89326.59±3163.78	p<0.001	0.856
	95% Confidenc	Lower Bound	5399.31	83080.71		
	Interval	Upper Bound	15058.59	95572.47		
Ghrelin7	Mean±Std. Error		1111.65±146.331	9029.70±783.63	p<0.001	0.713
	95% Confidence	Lower Bound	822.81	8667.23		
	Interval	Upper Bound	1400.48	9392.17		
Resistin7	Mean±Std. Error		4472.29±769.86	30217.67±1064.46	p<0.001	0.195
	95% Confidence	Lower Bound	2951.89	28115.47		
	Interval	Upper Bound	5992.69	32319.88		
Covariance analysis						

be 960 (400–4600) ng/ml on the 7th day. The Wilcoxon test identified a statistically significant difference between measurements of ghrelin levels on day 0 and day 7 ($p=0.023$, $p<0.05$). The values on day 7 were statistically lower than the values on day 0. The relationship of ghrelin values with BMI was assessed with Spearman's correlation analysis. No relationship was found. Table 1 illustrates the change in the patients' ghrelin levels based on days of abstinence.

Results Obtained from Evaluation of the Serum Resistin Levels

The median value of the resistin levels of patients was measured to be 2750 (560–10000) ng/ml on day 0 and 4000 (1100–10000) ng/ml on day 7. The Wilcoxon test showed a statistically significant difference between measurements of resistin levels on day 0 and day 7 ($p=0.000$, $p<0.05$). The values on day 0 were significantly lower compared to the values on the seventh day. The correlation of resistin values with BMI was tested with Spearman's correlation analysis and was found to be related. Taking the BMI effect into consideration, a time comparison was made with the covariance analysis and no statistically significant difference was found between the resistin levels on days 0 and 7. Table 1 illustrates the change of patients' resistin levels with respect to days of abstinence.

**Figure 1: Comparison of Adiponectin, Ghrelin, Resistin Levels of the Patient Group on Day 0 and 7 and Control Group**

Results Obtained from the Comparison of Patient and Control Groups

Comparing the day 0 and day 7 values of the patient group to those of the control group by using the Mann Whitney test, the adiponectin and ghrelin levels were statistically significantly different on both days. The values for the patient group on day 0 were found to be significantly higher compared to the values of the control group and even though the difference decreased by the 7th day, it continued to be significant between two groups ($p<0.01$). The resistin levels were statistically and significantly

higher on day 0 compared to the control group ($p < 0.01$); this difference continued in the values of the 7th day ($p < 0.01$). The relationship of the BMI values of the patient and control groups with three indicators was assessed using a covariance analysis and no significant relationship was determined (Table 2).

DISCUSSION

The purpose of this study was to examine the changes in serum adiponectin, ghrelin, and resistin levels in alcohol dependent patients within days of quitting and to compare them with a healthy control group. In this study, a statistically significant increase was determined in adiponectin and ghrelin levels, which are considered a biological condition-determining indicator during the withdrawal period of alcohol addicts, compared to the healthy control group. On the seventh day, both of the indicators showed a statistically significant decrease, but still the difference was significantly higher compared to the control group. While the resistin levels were significantly higher compared to the control group at the beginning of the withdrawal (day 0), they continued to be higher than control group values on the seventh day.

In recent years, the number of studies investigating the role of appetite-regulating peptides in the alcohol craving behavior in alcohol-dependent patients has increased. The majority of studies have focused on leptin and ghrelin. Considering the studies that have been conducted, it has been observed that ghrelin serum levels are statistically and significantly higher in alcohol-dependent patients (12,13). It has been indicated that the acute effect of ethanol intake decreases ghrelin in healthy volunteers (20,21). Different ghrelin levels have been shown in alcohol addicts during periods of active drinking, withdrawal, and sobriety. Addolorado showed that ghrelin levels were lower in active alcohol addicts compared to a control group (13, 22, 23) and there are studies that have demonstrated a significant increase following the withdrawal period (11,12). In this study, the ghrelin levels of the patient group that were measured in the beginning significantly decreased by the 7th day, when the detoxification treatment was ended. In contrast to the results of studies conducted by Addolorato et al., our result does not support the literature asserting that ghrelin levels in alcohol addicts have a tendency to increase after

withdrawal. In contrast to Addolorado, comparison of the ghrelin levels on the first day of treatment with those of the control group showed a significant increase in alcohol dependent patients compared to the control group and the ghrelin levels of the patients significantly decreased after the one-week detoxification treatment. In the study conducted by Kraus et al., it was indicated that ghrelin levels increased in patients with alcohol dependence and they increased even further during alcohol withdrawal. The study, in which Kim et al. previously compared sober alcohol addicts and healthy volunteers, also revealed that ghrelin levels increased throughout withdrawal (11). In addition to these, in this study, an increase was observed in ghrelin levels from the first day of sobriety during the one-week withdrawal period and even in those who had quit drinking alcohol one day before (12). In our study, the ghrelin levels were found to be high in alcohol dependent patients in the beginning compared to the control group, supporting the study of Kraus; however, they showed a significant decrease in contrast to the findings of Kraus after the detoxification treatment. However, in the study of Badaoui et al (2008), a decrease was observed on ghrelin levels in the plasma and fundus following alcohol withdrawal (23), supporting the results of our study.

Considering the differences between the results of the studies in the literature, this might be associated with the different ghrelin kits being used, nutritional status of the evaluated patients (body mass, lean mass, or energy consumption during the recovery) or the fact that they are in different drinking periods (active drinking vs. detoxification). Another reason for the differences of ghrelin levels might be associated with the fact that this peptide, which originates in the stomach, shows a very rapid regulation and a limited blood stability. In contrast to leptin, which is regulated slowly and is accepted to be the long-term indicator of energy consumption, ghrelin levels rapidly decrease after a meal intake. Ghrelin, which is known to antagonize the effects of leptin, is a neuropeptide that is thought to play an important role in alcohol dependence pathophysiology (24-26). It is thought that this antagonism occurs by means of the NPY and AGRP (Agouti Gene-Related Protein) systems, which are the key hypothalamic peptides located at the center of energy homeostasis. It has been shown that ghrelin strongly stimulates eating behavior following intracerebroventricular injection in rats and that their weights increased. It has

been demonstrated that acute alcohol withdrawal in rats decreased NPY expression in the amygdala and hypothalamus (27).

Studies have shown that NPY modulates anxiety by means of Y1 receptor activation in the amygdala and thus, it is an endogenous anxiolytic. During withdrawal, it has been demonstrated that the decrease of NPY in the amygdala increases the anxiety and relapse rates, as is expected (27). The direct relation of neurons that involve NPY with ghrelin has also been determined in the arcuate nucleus of the hypothalamus (11). The significant increase in ghrelin levels at the beginning of the withdrawal period in our study group might be an adaptation aimed at increasing the NPY level which decreased during this period. Regarding the sobriety period, on the other hand, it is reasonable that a decrease might have occurred in the ghrelin levels depending on the increasing NPY expression.

In addition to ghrelin, one other appetite-regulating peptide that is researched in alcohol dependence is adiponectin. Adiponectin plays a role in glucose metabolism, weight gain, and inflammation in atherogenic processes. In experimental animal studies, adiponectin injection caused weight loss and an increase in energy consumption without any decrease in food consumption. Studies on the central nervous system support the fact that adiponectin crosses the blood-brain barrier (8). It has been demonstrated that the hypothalamus contains adiponectin receptors (9). Considering these findings, adiponectin has been thought to play a role in appetite regulation in the central nervous system (8). In a study conducted by Hillemacher et al. in 2009, it was found that the adiponectin levels of alcohol addicts were significantly higher compared to the control group and a significant decrease was reported on the 7th day. Our study also supports the literature and while the adiponectin levels were significantly higher on day 0 compared to the control group, they showed a significant decrease on the 7th day. Considering the appetite regulation of adiponectin, the increased values in alcohol addicts could be associated with the malnutrition-causing effect of alcohol. The decrease in their levels following alcohol withdrawal, on the other hand, could be associated with the recovery from malnutrition under the effect of alcohol abstinence and detoxification treatments. Studies have revealed that nutritional disorders in alcohol addicts recover within at least 3 months following alcohol abstinence (28).

Unfortunately, the our patients could not be followed for more than one week and this could be interpreted as one of the limitations of the study. In addition, cigarette consumption affects adipocytokine expression and adiponectin levels have not been considered according to cigarette consumption in our study, which could be another limitation.

Another molecule that is being researched in alcohol-dependent patients is resistin which is one of the adipocytokines. It is synthesized by mononuclear cells and macrophages in white adipose tissue. In a general sense, it is accepted to function in the opposite direction to adiponectin. Studies have shown that the resistin gene is expressed in the hypothalamus and pituitary gland (14). In a study that was conducted in 2004, resistin was indicated to have an effect on dopamine and norepinephrine secretion from the hypothalamus (15). In a study which investigated adiponectin and resistin effects on the central nervous system, they were found to be significantly higher in alcohol-dependent patients during the active drinking period compared to a healthy control group and resistin levels continued to increase at statistically insignificant levels after the detoxification treatment (10). In our study, while the values on day 0 were significantly higher compared to the control group, they continued to increase on the 7th day compared to the control group, as well. Studies have indicated that resistin has an effect on mononuclear cells in the opposite direction to that of adiponectin (14). Our study results support these findings. While the adiponectin levels were found to be high in alcohol-dependent patients, they showed a tendency to decrease after detoxification. On the contrary, resistin increased significantly. Similar to our study, Hillmacher's study also concluded that resistin levels increased in alcohol-dependent patients after detoxification (10). There are a limited number of studies conducted on resistin in this field and there is a need for future studies about alcohol dependence and possible cravings.

CONCLUSION

In this study, while the adiponectin and ghrelin levels were significantly higher in patients with alcohol addiction compared to the control group at the beginning of the withdrawal treatment, they significantly decreased by the 7th day. Resistin levels, on the other hand, were determined

to have significantly increased in the beginning and they continued to be high on the 7th day.

To appraise the results of our study according to the results in the literature, we measured the levels of three adipocytokines (adiponectin, ghrelin, and resistin), which play a role in central appetite regulation and are asserted to possibly be associated with alcohol cravings, in alcohol addicts in our study. The three adipocytokine levels were found to have been affected in addicted patients. Comparing values of the patient group with the control group, even though there was a change compared to the values of the first day after the one-week alcohol detoxification, it was still different from the control group in a significant way. This result makes us think that the changes in the values might be associated with the features of dependence rather than the acute effects of alcohol. In addition to this, more

reliable results can be reached by following the patients and changes in the indicators for a longer period of time. Elucidating the relationship between indicators that play a role in appetite regulation and dependence and especially cravings, might light the way for studies to develop treatment strategies and prevent relapses.

Studies, in which the sub-typology of alcohol addicts is determined, the gender distribution is homogenous, nutritional status is assessed, and the periods of intoxication, withdrawal, sobriety, and craving are inclusively investigated, will give much more explicit results regarding this subject. In addition, the treatments aimed at decreasing the symptoms of craving and withdrawal might affect the hormone values and relations among the hormones. This possibility should be taken into consideration while determining methods of studies and evaluating results.

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