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The Effect of Treatment on Weight Gain in Iron Deficiency Anemia and Its Association with Ghrelin and Hepcidin Levels

Demir Eksikliği Anemisinde Tedavinin Kilo Alımına Etkisi ve Ghrelin ve Hepsidin Düzeyleri ile İlişkisi

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ABSTRACT

Aim: Although loss of appetite in iron deficiency anemia (IDA) and weight gain during treatment are common complaints, there are very few studies in adults. This study aimed to determine the levels of ghrelin, one of the appetite-related hormones, and hepcidin, one of the main regulators of iron metabolism, in IDA, and to examine the effects of treatment on weight gain and the levels of these hormones.

Material and Methods: Eighty-seven adult patients with IDA and a control group of 50 healthy volunteers were included in the study. Anthropometric measurements and blood samples were obtained from the patient and control groups before treatment, and repeated after treatment in the IDA group.

Results: No significant difference was found in terms of weight, body mass index (BMI), and waist-to-hip ratio between groups but there was a significant increase in weight and BMI, in the patient group after treatment (both $p<0.001$). Pre-treatment hepcidin and ghrelin levels of the patient group were significantly lower than the control group ($p<0.001$, and $p=0.026$, respectively), and hepcidin levels increased significantly after treatment ($p<0.001$). The increase in ghrelin was not statistically significant but showed a positive weak correlation with both weight ($r=0.254$, $p=0.018$) and BMI ($r=0.231$, $p=0.031$) increase. Hepcidin levels were not correlated with weight and BMI changes.

Conclusion: These findings revealed low levels of ghrelin and hepcidin in adults with IDA and an increase in weight and BMI with treatment. Hepcidin increased with treatment but was not correlated with weight gain, ghrelin was weakly correlated.

Keywords: Iron deficiency anemia; appetite; weight gain; ghrelin; hepcidin.

ÖZ

Amaç: Demir eksikliği anemisi (DEA)'nde iştahsızlık ve tedavi sırasında kilo alımı sık yakınmalar olsa da bu konuda erişkinlerde yapılmış çok az çalışma mevcuttur. Bu çalışmada, DEA'da iştah ile ilgili hormanlardan biri olan ghrelin ve demir metabolizmasının temel düzenleyicilerinden biri olan hepsidin seviyelerinin belirlenmesi ile tedavinin kilo alımına ve bu hormonların düzeylerine etkisinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Çalışmaya DEA tanılı 87 erişkin hasta ve 50 sağlıklı gönüllüden oluşan kontrol grubu dahil edildi. Hasta ve kontrol grubunda tedavi öncesi antropometrik ölçümler yapılarak kan örnekleri alındı ve tedavi sonrasında DEA grubunda tekrarlandı.

Bulgular: Gruplar arasında kilo, vücut kitle indeksi (VKİ), bel-kalça oranı açısından anlamlı fark yoktu ancak hasta grubunda tedavi sonrasında kilo ve VKİ'de anlamlı artış saptandı (her iki $p<0,001$). Hasta grubunun tedavi öncesi hepsidin ve ghrelin seviyesi kontrol grubuna göre anlamlı olarak daha düşüktü (sırasıyla $p<0,001$ ve $p=0,026$) ve tedavi sonrası hepsidin seviyeleri anlamlı olarak arttı ($p<0,001$). Tedavi sonrası ghrelin artışı istatistiksel olarak anlamlı değildi ancak hem kilo ($r=0,254$; $p=0,018$) hem de VKİ ($r=0,231$; $p=0,031$) artışı ile pozitif yönde zayıf korelasyon gösteriyordu. Hepsidin düzeylerinin kilo ve VKİ değişimleri ile korelasyonu saptanmadı.

Sonuç: Bu bulgular erişkinlerde DEA'da ghrelin ve hepsidinin düşük olduğunu ve tedavi ile hastalarda objektif bir kilo ve VKİ artışı olduğunu ortaya koydu. Hepsidin tedavi ile artış göstermekle beraber kilo alımı ile korele değildi, ghrelin zayıf korelasyon göstermekteydi.

Anahtar kelimeler: Demir eksikliği anemisi; iştah; kilo alımı; ghrelin; hepsidin.

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INTRODUCTION

Anemia is accepted as a worldwide public health problem by the World Health Organization (WHO) and iron deficiency anemia (IDA) is the most common type of anemia (1). IDA, which constitutes approximately 50% of all anemias (2), is an anemia that develops as a result of decreased erythropoiesis due to a significant decrease in the total amount of iron, which is essential for hemoglobin (Hb) production (3). In the patient management, investigation and, if possible, correction of the condition causing iron deficiency has an important place and iron replacement by oral or parenteral route is the treatment of choice. Although this treatment seems to be simple, problems are frequently encountered especially in compliance with oral iron treatment and it has been shown that the drugs are not used regularly or discontinued because of gastrointestinal complaints or weight gain during the treatment process (4). Although increased appetite and weight gain during iron therapy is a common complaint heard by clinicians, there are very few publications on the objective demonstration and causes of this.

Ghrelin and hepcidin are parameters related to appetite and iron metabolism associated with iron deficiency which have been investigated in recent years (5). Ghrelin is a hormone secreted from the gastric fundus that stimulates the feeling of hunger. It increases appetite and food intake centrally or peripherally (6). Hepcidin is a homeostatic regulator of iron absorption from the intestine. Increases in plasma iron levels and increases in tissue iron deposits activate hepcidin synthesis and then hepcidin decreases iron release from macrophages and enterocytes (7). There are studies reporting a significant increase in hepcidin and ghrelin levels with iron treatment in children (8). There are many studies reporting low ghrelin levels in the presence of IDA in children and associating this with anorexia (9,10). Increased ghrelin levels, weight gain, and acceleration in growth have also been reported with iron treatment in children (11-13). However, studies on whether there is an objective weight gain with treatment in adults and its determinants are limited and contradictory (14,15).

We planned this study to determine the levels of ghrelin, one of the hormones related to appetite, and hepcidin, one of the main regulators of iron metabolism, and the effect of treatment on weight gain and the levels of these hormones in IDA. We hope that this study will provide information that will contribute to explaining the decreased appetite seen in IDA and the compliance problems experienced during treatment.

MATERIAL AND METHODS

This study, which was approved by the decision numbered 2015/63 of the local Ethics Committee of Duzce University on 02.11.2015 and supported by the Scientific Research Projects Coordinatorship of Duzce University (Project no: 2015.04.03.396) was carried out in accordance with the principles of the Declaration of Helsinki. A total of 130 patients over the age of 18 who were admitted to the Internal Medicine or Hematology outpatient clinic of our hospital, who were diagnosed with IDA according to WHO and Turkish Hematology Association criteria (Hb <13 g/dl in males, Hb <12 g/dl in females, and ferritin <15 ng/mL) were evaluated for the study. Patients who are younger than 18 years of age or pregnant, who have received erythrocyte or whole blood transfusion in the last 3 months, who have used oral or parenteral iron preparations in the last month, who have any of the etiological causes that may cause anemia other than iron deficiency (vitamin B12 or folate deficiency), and patients with active inflammatory or infectious diseases, with another hematological disease (thalassemia, myelodysplastic syndrome, multiple myeloma, chronic myeloproliferative disease, etc.) or who did not give consent (43 subjects in total) were excluded from the study. After obtaining the consent of 87 IDA patients and 50 healthy volunteers, weight, height, body mass index (BMI), waist and hip circumference were measured and blood samples were taken. The patients were treated for iron deficiency with the dose and method (orally or parenterally) recommended by the responsible doctor, and the researchers had no influence on the treatment. After the Hb and mean corpuscular volume (MCV) levels were normalized and ferritin was >30 ng/mL according to the anemia parameters of the patient being followed up in the outpatient clinic, but not before the 3rd month of treatment, weight, height, waist and hip circumference were measured and blood samples were taken again.

Venous blood was collected from the patient and control groups (IDA patients before and after treatment, and from the control group only once) at 08:00-09:00 hours after 8 hours of fasting. For biochemical parameters, appropriate amounts of samples were collected using serum tubes containing a clot activator with a separator. Biochemical parameters, urea, creatinine, sodium, potassium, ferritin, iron, and total iron binding capacity (TIBC) were determined on ROCHE COBAS 6000 Hitachi c501 (Roche Diagnostics GmbH, Mannheim, Germany) auto analyzer using commercial kits (Roche Diagnostics, Germany) and hemogram was determined on the same day without waiting on BECMAN COULTER LH 780 (USA) using commercial kits. For hepcidin and ghrelin levels, samples were centrifuged by a single physician, serum was separated, portioned into Eppendorf tubes, and stored at -80 °C. Hepcidin was analyzed by the enzyme-linked immunosorbent assay (ELISA) method using Elabscience Biotechnology Co., Ltd (Wuhan, P.R.C.) brand Human Hepcidin-25 (bioactive) ELISA kit (REF: E-EL-H0077-96 Wells) according to the manufacturer's catalog. Ghrelin was analyzed in serum samples using Elabscience Biotechnology Co., Ltd (Wuhan, P.R.C.) brand Human Acylated Ghrelin ELISA kit (REF: E-EL-H1919-96 Wells) in Biotec L800 device according to the manufacturer's catalog.

Statistical Analysis

Descriptive statistics were presented as mean, standard deviation or median, first and third quartiles, and frequency and percentage, as appropriate for the type of data. The conformity of numerical data to the normal distribution was examined with the Kolmogorov-Smirnov test. The independent-sample t-test or Mann-Whitney U test was used to compare numerical variables between groups. Relationships between categorical variables were analyzed using Pearson's chi-square and Fisher's exact tests. Paired samples t-test or Wilcoxon test was used to

compare variables before and after treatment. The statistical significance level was taken as 0.05 and PASW v.18 was utilized for statistical analyses.

RESULTS

A total of 137 people, including 87 patients and 50 control, were included in the study. Parameters such as age, hemogram and anemia parameters, vitamin B12, folate, BMI, waist and hip circumference, waist-to-hip ratio, hepcidin, and ghrelin levels were evaluated in iron deficiency patients and control group, and details were given in Table 1. Females constituted 81.6% (n=71) of the patient group and 82.0% (n=41) of the control group and there was no statistically significant difference between the groups (p=0.955). The mean Hb level was 9.59±1.72 gr/dl, the MCV value was 69.38±7.29 fl, and the ferritin value was 6.57±3.32 ng/mL, and these values indicated significant iron deficiency. Other anemia parameters were significantly different from the control group (p<0.001) in accordance with IDA. BMI, waist-to-hip ratio, white blood cell (WBC), vitamin B12, and folate levels were not significantly different between the patient and control groups (Table 1).

When the pre- and post-treatment examinations of the patient group were compared, there was no significant difference in WBC values, but there was a significant increase in Hb and anemia-related parameters indicating the effectiveness of the treatment (Table 2). No significant difference was found between the pretreatment vitamin B12 and folate levels and the control group.

When the pre-treatment and post-treatment measurements were evaluated, it was found that the weight, BMI, waist and hip circumference measurements of the patients increased significantly, the patients gained an average of 1.15 kg after treatment (p<0.001), BMI increased from 25.86 kg/m^2 to 26.33 kg/m^2 (p<0.001), both waist and hip circumference increased significantly (0.81 cm increase for waist and 0.82 cm increase for hip, respectively, p<0.001), but the waist-to-hip ratio remained constant. While ferritin, iron, and transferrin saturation (TSAT) values increased significantly after treatment, TIBC decreased significantly (Table 2).

The pretreatment hepcidin level was 80 ng/ml in IDA patients and 179 ng/ml in the control group and was found to be statistically significantly (p<0.001) lower in IDA. Similarly, the ghrelin level was found to be 152 pq/ml in patients with IDA and 213 pq/ml in the control group and was found to be statistically significantly (p=0.026) lower in the IDA group.

When compared before and after treatment in patients, plasma hepcidin levels increased significantly (80 ng/ml and 92 ng/ml, respectively, p<0.001). The plasma ghrelin level was found 152 pq/ml before treatment and 164 pq/ml after treatment, but this increase did not reach statistical significance (p=0.589).

When the correlations of the change in weight and BMI of the patients with the change in anemia parameters or ghrelin and hepcidin levels were investigated, both weight and BMI changes were found to be positively correlated only with ghrelin change, albeit weakly (r=0.254, p=0.018 for weight change and r=0.231, p=0.031 for BMI change). No significant correlation was found with the change in anemia parameters or change in hepcidin level.

Table 1. Comparison of demographic and clinical characteristics in patients with IDA and control group

	IDA (n=87)	Control (n=50)	p
Gender, n (%)			
Female	71 (81.6)	41 (82.0)	0.955
Male	16 (18.4)	9 (18.0)	
Age (year)	42.74±15.09	41.22±13.14	0.554
WBC (x10^9/L)	6.99±1.75	6.87±1.37	0.672
Hb (g/dl)	9.59±1.72	13.48±1.27	**<0.001**
MCV (fl)	69.38±7.29	85.56±2.42	**<0.001**
Ferritin (ng/ml)	6.57±3.32	58.23±37.90	**<0.001**
Iron (mcg/dL)	25.86±11.14	83.92±26.85	**<0.001**
TIBC (mcg/dL)	413.47±65.52	246.78±40.71	**<0.001**
TSAT (%)	6.45±3.24	34.87±13.29	**<0.001**
B12 (pg/ml)	441.14±319.78	349.26±115.61	**0.017**
Folate (ng/ml)	10.39±4.56	10.05±4.27	0.667
BMI (kg/m^2)	25.86±6.21	25.13±4.60	0.472
WHR	0.7647±0.0789	0.8628±0.5128	0.082

IDA: iron deficiency anemia, WBC: white blood cell, Hb: hemoglobin, MCV: mean corpuscular volume, TIBC: total iron binding capacity, TSAT: transferrin saturation, B12: vitamin B12, BMI: body mass index, WHR: waist to hip ratio

Table 2. Comparison of anemia parameters and anthropometric measurements before and after treatment in patients with IDA

	Before	After	p
WBC (x10^9/L)	6.99±1.75	7.20±1.91	0.319
Hb (g/dl)	9.59±1.72	13.14±1.01	**<0.001**
MCV (fl)	69.38±7.29	82.64±7.58	**<0.001**
Ferritin (ng/ml)	6.57±3.32	106.81±135.57	**<0.001**
Iron (mcg/dL)	25.86±11.14	82.51±54.59	**<0.001**
TIBC (mcg/dL)	413.47±65.52	254.94±63.76	**<0.001**
TSAT (%)	6.45±3.24	42.19±68.01	**<0.001**
Weight (kg)	68.30±15.83	69.45±16.10	**<0.001**
BMI (kg/m^2)	25.86±6.21	26.33±6.34	**<0.001**
WC (cm)	80.33±14.38	81.14±14.61	**<0.001**
HC (cm)	104.52±10.94	105.34±11.40	**<0.001**
WHR	0.7647±0.0789	0.7664±0.0780	0.071

IDA: iron deficiency anemia, WBC: white blood cell, Hb: hemoglobin, MCV: mean corpuscular volume, TIBC: total iron binding capacity, TSAT: transferrin saturation, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist to hip ratio

DISCUSSION

Anemia is a worldwide public health problem, approximately 25% of the world population is anemic, concentrated in preschool-aged children and women (16). Even though different etiologies come to the fore according to age groups in IDA, which is the most common cause of anemia, the most important cause in developing countries, as in Türkiye, is inadequate intake of iron-containing foods (9). On the other hand, one of the clinical findings of IDA observed by clinicians is decreased appetite and this may turn the condition into a vicious cycle.

The association of IDA with appetite, nutrition, and weight gain has been investigated primarily in children and adolescents. In a study by Naiman et al. (17) on 14 infants and children, the gastrointestinal systems of children with IDA were analyzed in detail including duodenal biopsies, and both functional and structural abnormalities were described. The fact that most of these abnormalities disappeared after iron treatment suggested that it caused diffuse and reversible enteropathy in children. In adolescent girls, a change in eating habits was observed with iron treatment given every other day, and a median weight gain of 2.66 kg was reported (12).

In our study, no significant difference was found in terms of weight when the patient and control groups were compared, but a statistically significant weight gain was found in the patient group with treatment in accordance with clinical experience and data in the literature on pediatric patients. This finding suggested that iron deficiency alone was not associated with low weight but iron treatment was associated with weight gain. In our study, BMI, waist and hip circumference, which are considered to be more objective indicators of subcutaneous and total body fat, increased significantly and it was shown that fat distribution was proportional according to the waist-to-hip ratio, which remained constant.

One of the parameters studied in the literature to reveal the causes of anorexia observed in IDA with objective measurements is ghrelin, which is also called the "appetite hormone". Ghrelin is a hormone released from the gastrointestinal system and is known to induce a feeling of hunger. Ghrelin hormone has orexigenic and adipogenic effects and is secreted in response to hunger and hypoglycemia (18). Endogenous ghrelin is a potentially important new regulator of complex systems controlling food intake and body weight (19). However, appetite has both biological and behavioral/psychological aspects and is difficult to assess quantitatively (20). Since appetite is a conscious desire for food, evaluation of the weight gained by measuring the amount of food eaten per day may be a way of measuring appetite. In a study by Shiiya et al. (21), 70 patients and 28 control groups were included and it was shown that plasma ghrelin concentration and BMI were negatively correlated. Many studies have been conducted to explain the association between iron and ghrelin levels. In a study conducted by Isguven et al. (9) in prebubertal children, 25 IDA and 25 control groups were included and ghrelin levels were found to be lower in children with IDA compared to the control group. Again, Akarsu et al. (10) investigated ghrelin levels in various periods of iron deficiency including hypoferritinemia, iron deficiency, and overt IDA in children, and reported that ghrelin levels decreased as iron deficiency became apparent. However, two more recent studies conducted in adults suggested findings in the opposite direction. Luo et al. (14) suggested that ghrelin increased with fasting in rats and healthy volunteers but iron levels decreased and there was a negative correlation between them. In their study in which 56 adult IDA patients and 51 healthy volunteers were examined, Ghrayeb et al. (15) reported that low Simplified Nutritional Appetite Questionnaire (SNAQ) scores indicated anorexia in the IDA group and acylated ghrelin (AG) levels and acylated ghrelin/unacylated ghrelin (AG/UAG) ratios were higher than in the control group. They reported that there was a significant increase in SNAQ scores and a significant decrease in AG levels and AG/AUG ratio after parenteral iron sucrose treatment was given to this patient group.

In our study, ghrelin level was found to be lower in patients with IDA compared to the control group, supporting the findings in studies conducted in children. In our study, the patient and control groups did not differ in terms of weight and BMI. This situation ensured that ghrelin changes which may be related to the effect of BMI were not a confounding factor and suggested that the decrease in ghrelin was an effect of iron deficiency. In other studies, decreased ghrelin levels were accompanied by lower weight and BMI values compared to the control group, but this difference with the other studies may have resulted from the age difference of the patient groups and the difference in sample sizes. However, our study reached different results from the study of Ghrayeb et al. (15), which is another longitudinal study conducted in adults. In this study, it is noteworthy that the BMI of the IDA group was higher than that of the control group and the gender distribution was different between the groups, but the authors also reported similar results with multivariate linear regression analysis. Since acylated ghrelin, which is thought to be the active form, was measured both in our study and in the study of Ghrayeb et al. (15), more extensive studies are required to clarify this issue.

In our study, although there was an increasing trend in ghrelin levels before and after treatment, this numerical increase did not reach statistical significance. This may be because ghrelin plasma concentration is negatively correlated with weight and BMI. In our study, weight and BMI increased significantly after treatment and it is known that weight gain suppresses ghrelin levels (22). Therefore, an increase in ghrelin may not have been seen as a net effect. When the association between the increase in ghrelin level of each patient and the weight gain of that patient was analyzed, a weak positive correlation was found.

Another parameter closely related to iron metabolism which has been studied recently is hepcidin. Hepcidin is mostly synthesized from the liver, but it has been shown that it is also synthesized from the kidneys, skeletal muscle, brain, and heart (23). Hepcidin is defined as the main homeostatic regulator of iron absorption in the intestines, the iron cycle in macrophages, and iron release from hepatic stores (24). The observation that hepcidin synthesis increased with dietary iron suggested that hepcidin was involved in iron metabolism, and it was shown that hepcidin level was a negative regulator of intestinal iron absorption, iron transport through the placenta, and iron release from macrophages (25).

Many studies have been performed to demonstrate the metabolism of hepcidin and iron. Dallalio et al. (26) showed a positive correlation between hepcidin and ferritin in patients with anemia. In a study where 94 patients with IDA and 91 control groups were included, it was found that hepcidin level was lower in the patient group with IDA compared to the control group (27). The largest studies performed with hepcidin to date are two large studies including 2998 patients in the Netherlands and 1577 patients in Italy. In these studies, hepcidin level was found to be low in correlation with low serum ferritin levels in premenopausal and postmenopausal women (28,29).

In our study, similar to these studies, when IDA and the control group were compared, there was a significant decrease in the level of hepcidin in the group with IDA compared to the control group. Since hepcidin expression in normal erythropoietic activity is directly related to hepatic iron stores, hepcidin expression is expected to increase when hepatocyte iron stores increase (30). Increased hepcidin levels have been reported with treatment in children who presented with IDA (31). In our study, pre-treatment hepcidin level was compared with post-treatment hepcidin level in patients with IDA, and a significant increase in post-treatment hepcidin level was found in support of these studies in the literature.

Although it has been suggested that hepcidin may have an effect on appetite and energy balance in iron deficiency, there are very few studies investigating this. It has been reported that some foods may have an effect on hepcidin levels (32), however, it is not clear whether the level of hepcidin affects food intake and through which pathways. In a study conducted in patients with newly diagnosed diabetes mellitus after pancreatitis without overt iron deficiency, a significant negative correlation of hepcidin with leptin, another determinant hormone of energy balance, and with leptin/ghrelin ratio in fasting was shown, but it was reported that it was not correlated with ghrelin (33). On the other hand, a study conducted in children with IDA reported that ghrelin and hepcidin levels were higher than controls before treatment, there was no difference in leptin levels and there was a significant increase only in hepcidin and ghrelin levels with treatment (31). Our study is the first study in the literature to investigate ghrelin and hepcidin changes together with weight changes in adults with IDA. In our study, weight change was not associated with parameters such as Hb, MCV, ferritin, and TSAT, which reflect the depth of anemia at baseline. Hepcidin, which was significantly lower than the pretreatment control and increased significantly with treatment, did not correlate significantly with either weight gain or BMI. These findings suggested that hepcidin is an important parameter that may contribute to the diagnosis of iron deficiency and may be used to show the adequacy of treatment, but it is not directly related to weight gain. Since hepcidin was significantly lower than in the control group, it seems possible that it has a role in the anorexia symptom seen in IDA patients, but large studies including other parameters related to appetite and energy balance may be necessary to clarify this role.

CONCLUSION

These findings suggested that decreased appetite, one of the symptoms frequently observed by clinicians in IDA, may be related to ghrelin levels, which were found to be lower in IDA patients compared to the control group. In our study, IDA patients, who were not different from the control group in terms of weight and BMI at baseline, showed a significant increase in weight and BMI with treatment, and the effect of treatment on weight gain attributed to treatment was demonstrated concretely. The increase in ghrelin with treatment did not reach statistical significance. This may be due to physiological suppression of ghrelin levels with weight gain. When weight gain was analyzed on a patient basis, a positive correlation was found with the increase in ghrelin. Hepcidin was significantly lower in the iron deficiency group compared to the control group and showed a significant increase with treatment, but was not associated with weight gain. Hepcidin can be considered as a parameter that can contribute to the diagnosis of iron deficiency and can be used to show the adequacy of treatment, but we did not find a direct relationship between hepcidin and appetite or weight gain. Although the results of our study overlap with the studies conducted in children, since contrasting findings were found with other recent adult studies, larger studies including other appetite-related hormones are needed to clarify the issue.

Ethics Committee Approval: The study was approved by the Ethics Committee of Düzce University Faculty of Medicine (02.11.2015, 63).

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