



ARAŞTIRMA / RESEARCH

Association between leptin and weight gain in patients receiving iron treatment

Demir tedavisi alan hastalarda leptin ve kilo alımı arasındaki ilişki

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Abstract

Purpose: The aim of this study was to evaluate the relationship between leptin and weight gain in patients receiving iron treatment.

Materials and Methods: A total of 42 female patients who were diagnosed with IDA were included in the study. Whole blood count, serum iron, serum unsaturated iron binding capacity (UIBC), serum ferritin level were measured at the time of diagnosis and on month one after treatment; serum hepcidin level and serum leptin level were measured at the time of diagnosis and 96 hours after commencement of parenteral therapy; body weight and appetite alterations were recorded at the time of diagnosis and on month one.

Results: A statistically significant difference was not found between hepcidin and leptin values at the time of diagnosis and after treatment. Increased appetite was detected in 22 (52.4%) patients on month one after treatment. While mean weight of all patients was 69.6±17.9 kg at the time of diagnosis, it was 70.7±17.5 kg on month one after treatment and there was a statistically significant difference between two values.

Conclusion: Our study revealed that appetite and body weight increased following iron therapy, consistently with our observations and hypothesis. However no significant relationship was found with leptin levels and weight increase.

Key words: Iron, leptin, hepcidin, weight gain

Öz

Amaç: Bu çalışmanın amacı demir tedavisi alan hastalarda leptin ve kilo artışı arasındaki ilişkiyi saptamaktır.

Gereç ve Yöntem: Toplamda 42 demir eksikliği anemisi tanısı konulan kadın hasta çalışmaya dahil edilmiştir. Tanı anında ve tedavi başladıktan 1 ay sonra tam kan sayımı, serum demir, ansature demir bağlama kapasitesi ve ferritin seviyesi, tanı anında ve tedavi başladıktan sonra 96. saatte serum hepsidin ve leptin seviyesi ölçüldü. İştahta meydana gelen değişiklikler ve vücut ağırlığı tanı anında ve tedavi başladıktan 1 ay sonra değerlendirildi.

Bulgular: Tanı anındaki ve tedavi başladıktan sonraki serum hepsidin ve leptin seviyeleri arasında istatistiksel olarak anlamlı fark bulunmadı. 22 (%52.4) hastada iştah artışı olduğu tespit edildi. Tanı anında hastaların ortalama ağırlığı 69.6±17.9 kg olarak tespit edilmiş iken tedavi başladıktan 1 ay sonra hastaların ağırlığı 70.7±17.5 kg olarak bulunmuştur ve değerler arasında istatistiksel olarak anlamlı fark tespit edilmiştir.

Sonuç: Çalışmamız gözlemlerimiz ve hipotezimizle uyumlu olarak demir tedavisini takiben hastalarda iştah artışı ve ağırlık artışı meydana geldiği saptanmıştır. Leptin düzeyleri ile kilo artışı arasında bir ilişki bulunmamıştır.

Anahtar kelimeler: Demir, hepsidin, leptin, kilo artışı

INTRODUCTION

Anemia is an important health problem in all age

groups¹. Iron deficiency anemia (IDA) is the most common type of anemia², and responsible for approximately 50% of anemias across worldwide³. IDA is present in more than 1.5 billion individual

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worldwide⁴. According to the estimations of World Health Organization (WHO), 42% of pregnant women, 30% of non-pregnant women between ages 15-50, 47% of pre-school children (0-5 years) and 12.7% of male above 15 years are anemic³.

Iron has been used for treatment of anemia for longer than 300 years⁵. Oral iron therapy is an effective, safe and inexpensive method^{6,7}. However parenteral iron treatment is required instead of oral iron therapy under some conditions. Both treatment methods have some well-known side effects. Gastrointestinal side effects like nausea, heartburn, abdominal pain, diarrhea, constipation, metallic taste are the well-known side effects of oral iron therapy^{6,7}. Late side effects mimicking serum disease like hypotension, urticaria, nausea, fatigue, musculoskeletal pain, lymphadenomegaly and anaphylaxis are the well-known side effects of parenteral iron therapy^{6,7}. Despite the presence of anxiety and observations about body weight increase in clinical practice, sufficient data are not available about this issue. The main role of leptin which is synthesized mainly in adipose tissue is to regulate food intake and energy metabolism through the suppressive effect on brain (particularly hypothalamus) and to prevent obesity, namely it works as a satiety factor^{8,9}. Hepcidin is a peptide hormone which regulates iron balance¹⁰. Hepcidin synthesis is stimulated by the increase of plasma iron levels and tissue iron deposits and it reduces iron release to plasma from macrophages and duodenal enterocytes^{11,12}. Erythropoietic stimulants reduce hepcidin production in case of anemia or hypoxia, eliminate the inhibitor effect hepcidin on iron absorption and iron release from macrophages, enable more iron to be used for erythropoiesis^{11,12}.

In some recent studies, a relationship has been shown between the hormones affecting on appetite center and hepcidin^{13,14}. Therefore, we planned this study under the light of these data considering that leptin levels may decrease together with the increase in hepcidin levels following iron therapy, potential appetite increase and body weight increase may be explained with this mechanism.

MATERIALS AND METHODS

This study was approved by Cumhuriyet University Ethics Committee (Project no: 2014-02/08; Date: 02/17/2014). All procedures performed in studies involving human participants were in accordance

with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study population

This is a prospective, multi-center study. Patient selection is clinical-based and independent from etiology. A total of 42 female patients who were diagnosed with IDA according to WHO diagnostic criteria (hemoglobin <12 g/dL, serum ferritin level <15 ng/mL, and/or transferrin saturation <16%), administered parenteral iron therapy were included in the study. The patients who had severe endocrinologic, psychiatric, oncologic diseases, vitamin B₁₂ or folate deficiency beside iron deficiency, using any medications which could influence appetite center and/or body weight were excluded from the study.

Laboratory and clinical evaluation

Whole blood count, serum iron, serum unsaturated iron binding capacity (UIBC), serum ferritin level were measured at the time of diagnosis and on month one after treatment; serum hepcidin level and serum leptin level were measured at the time of diagnosis and 96 hours after commencement of parenteral therapy; body weight and appetite alterations were recorded at the time of diagnosis and on month one.

Serum iron, serum unsaturated iron binding capacity (UIBC) were studied using ferrozin method (Roche Diagnostics GmbH, Mannheim, Germany), serum ferritin level was studied using immunoturbidimetric method (Roche) and Cobas e 601 immunoassay analyzer (Roche). Transferrin saturation index was calculated using the formula: serum iron/total iron binding capacity (UIBC) x 100. Serum hepcidin level (Hangzhou Eastbiopharm Co., Ltd., China) and leptin level (eBioscience, Bender MedSystems GmbH, Vienna, Austria) were measured using ELISA kit before treatment and at 96th hour. Whole blood count of all patients was studied using Coulter LH 750 hematology analyzer (Beckman-Coulter, Brea, CA, USA).

Treatment protocol

The patients were treated with 2700-5400 mg iron

(Fe³⁺) hydroxyl sucrose complex equal to 100-200 mg elemental iron by intravenous infusion at every other day according to the needs of the patients (a total of 3-5 doses).

Statistical analysis

Patient characteristics were evaluated using descriptive statistics. Continuous variables were given as mean \pm standard deviation; categorical variables were given as percent. Chi-square and student's t-test were used for comparison of percent

and mean values. A p level of <0.05 was accepted as statistically significant. SPSS (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) program was used for all statistical calculations.

RESULTS

Mean age was found as 36.2 ± 9.2 years. Data of the patients about whole blood count and iron parameters before treatment and at month one after treatment are given in Table 1.

Table 1. Pre-treatment and post-treatment data of the patients

Parameter	Pre-treatment	Post-treatment (1st month)
Leukocyte ($\times 10^3 / \mu\text{L}$)	6.7 ± 1.7	6.3 ± 1.2
Erythrocyte ($\times 10^{12} / \text{L}$)	4.42 ± 0.46	4.90 ± 0.36
Hemoglobin (g/dL)	8.4 ± 1.3	11.5 ± 1.0
Hematocrit (%)	27.7 ± 3.6	36.0 ± 2.7
MCV (fL)	62.7 ± 5.7	73.6 ± 4.7
Platelet ($\times 10^9 / \text{L}$)	355 ± 128	311 ± 90
Iron ($\mu\text{g}/\text{dL}$)	19.9 ± 5.7	58.1 ± 22.2
UIBC ($\mu\text{g}/\text{dL}$)	443.5 ± 52.0	329.9 ± 54.3
Ferritin (ng/mL)	4.6 ± 2.6	56 ± 33.3

MCV: mean corpuscular volume; UIBC: unsaturated iron binding capacity

Hepcidin and leptin values before treatment and 96 hours after treatment are given in Table 2. A statistically significant difference was not found between hepcidin and leptin values at the time of diagnosis and after treatment. A correlation was detected between hepcidin and leptin values considering the variation between levels at the time of diagnosis and after treatment ($r = -0.27$, $p = 0.867$). Increased appetite was detected in 22 (52.4%)

patients on month one after treatment. While mean weight of all patients was 69.6 ± 17.9 kg at the time of diagnosis, it was 70.7 ± 17.5 kg on month one after treatment and there was a statistically significant difference between two values ($p < 0.001$). In addition, a poor correlation was detected between weight increase and variation in hepcidin values ($r = 0.123$, $p = 0.439$), between weight increase and variation in leptin values ($r = -0.064$, $p = 0.685$).

Table 2. Hepcidin and leptin values before treatment and 96 hours after treatment

Parameter	Before treatment	After treatment	P value
Serum Hepcidin (g/L)	51.2 ± 42.7	64.5 ± 53.1	0.092
Serum Leptin (pg/mL)	368.2 ± 278.5	333.2 ± 233.8	0.258

DISCUSSION

Individuals with iron deficiency have appetite loss, while dietary iron supplementation is associated with increased appetite in children¹⁵. The mechanism underlying these associations is poorly understood¹⁵. Therefore, we investigated the effect of iron on appetite and body weight associated with leptin. Results of our study revealed the influences of iron

therapy on appetite and body weight increase. Serum hepcidin level was observed to increase and serum leptin level was observed to decrease after commencement of iron therapy, although results were not statistically significant. Similarly to our study, Doğan et al.¹³ detected an increase in serum hepcidin level and a decrease in serum leptin levels, although statistically insignificant in their study conducted with 30 children with IDA. Serum

ghrelin level was also examined in their study and it was detected to increase¹³. There are some differences between this study and our study; the patient populations composed of children, oral iron therapy was preferred, and level of ghrelin which is the contra-regulatory hormone of leptin and known as fasting hormone was examined. Detection of a reduction in serum leptin level and an increase in serum ghrelin level supports the close relationship between iron therapy and appetite-regulating hormones.

Aukett et al.¹⁶ designed to determine the effect of psychomotor development of giving oral treatment. In this study toddlers with anemia who received treatment with iron for two months when compared with a control group with anemia who did not receive treatment with iron were different in two respects¹⁶. Aukett et al.¹⁶ detected a weight increase more than expected in iron therapy-receiving group compared to control group however they did not make an investigation about the mechanism of effect. Differently from our study, serum hormone levels were not examined in that study and the study conducted in children.

In a current study, Gao et al.¹⁵ determined that dietary iron overload increases adipocyte iron and decreases mRNA and serum protein levels, and consequently iron-induced downregulation of leptin is associated with increased food intake in mice. They also found that human ferritin levels are inversely associated with serum leptin independently of inflammation and BMI¹⁵. Gao et al. have shown a reverse relationship between iron intake and leptin in their animal study, supporting our hypothesis. The human part of that study has focused on only the relationship between serum ferritin and leptin levels, but the influence of iron treatment on appetite and weight gain was not investigated, differently from our study. The major limitations of this study was small patient population of our study and potential difficulties for serum leptin level measurement (short half-life, diurnal and pulsatile secretion).

In conclusion, sufficient and clear data are not available about this issue and we think that this effect of iron treatment is overlooked. Our study revealed that appetite and body weight increased following iron therapy, consistently with our observations and hypothesis. We consider that revealing the influence of iron therapy on appetite

and body weight through larger and well designated studies would provide more data.

REFERENCES

1. Aypak C , Çakmak N, Görpeliöđlu S. An unusual cause of anemia: Cameron ulcer. *Cukurova Medical Journal*. 2013;38:315-8.
2. Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. *Blood*. 2014;123:326-33.
3. Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA. Control of iron deficiency anemia in low- and middle-income countries. *Blood*. 2013;121:2607-17.
4. Asma S, Gerekliöđlu Ç, Erdoğan AF, Yeral M, Kasar M, Bođa C et al. Prevalence of iron, folic acid and vitamin B12 deficiency in patients with thalassemia minor. *Turkish Journal of Family Medicine Primary Care*. 2013;7:83-6.
5. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program*. 2010;2010:338-47.
6. Shah A. Iron deficiency anemia-Part III. *Indian J Med Sci*. 2004;58:214-6.
7. Patil SS, Khanwelkar CC, Patil SK. Conventional and newer oral iron preparations. *IJMPS*. 2012;2:16-22.
8. Denver RJ, Bonnett RM, Boorse GC. Evolution of leptin structure and function. *Neuroendocrinology*. 2011;94:21-38.
9. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY et al. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab*. 2011;301:E567-84.
10. Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. *J Clin Invest*. 2013;123:2337-43.
11. Camaschella C. Iron and hepcidin: a story of recycling and balance. *Hematology Am Soc Hematol Educ Program*. 2013;2013:1-8.
12. Bařol G, Barutçuođlu B, Bozdemir AE. Hepcidin, a new regulator of iron homeostasis. *J Turkish Clinical Biochemistry*. 2007;5:117-25.
13. Dođan A, Aliođlu B, Dindar N, Dallar Y. Increased serum hepcidin and ghrelin levels in children treated for iron deficiency anemia. *J Clin Lab Anal*. 2013;27:81-5.
14. Chung B, Matak P, McKie AT, Sharp P. Leptin increases the expression of the iron regulatory hormone hepcidin in HuH7 human hepatoma cells. *J Nutr*. 2007;137:2366-70.
15. Gao Y, Li Z, Gabrielsen JS, Simcox JA, Lee SH, Jones D et al. Adipocyte iron regulates leptin and food intake. *J Clin Invest*. 2015;125:3681-91.
16. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child*. 1986;61:849-57.