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Research Article / Araştırma Makalesi

Is Iron Deficiency A Cause of Chronic Inflammation?

Demir Eksikliği Kronik Inflamasyonun Bir Nedeni midir?

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Abstract

Iron is an essential mineral requiredfor a variety of vitalbiologicalfunctions. C-reactive protein (CRP) is widelyused as a routine marker of chronicoracuteinflammation. Bothirondeficiencyandexcessinduceproinflammatoryactivity in the body. Weclinicallyobservedthat C-reactive protein, whichwashighbeforeirontreatment, decreasedafterirontreatment. Weaimedtoinvestigatetheauthenticity of thisclinicalobservationandcompareourresultswiththeliterature. Inthissingle-center, prospectivestudy, 170 femalepatients of reproductiveagewhowerefoundtohaveirondeficiencyanemiaaccordingtothe 2001 WHO irondeficiencycriteriawereincluded in thisstudy, withtheapproval of theethicscommittee. Hemoglobin, hematocrit, meancorpuscularvolume, leukocyte, platelet, ferritin, folate, C-reactive protein valueswererecorded at the time of firstadmissionand 4-8 weeksafterthetreatment. An increase in thelevels of mean hemoglobin (11.7±1.4 vs 9.5±1.7; p<0.001), mean HCT (36.0±3.6 vs 30.7±4.7; p<0.001), mean MCV (76.7±7.8 vs 70.0±9.2; p<0.001), andmedianferritin (43 vs 3.6; p<0.001) wasobserved in additionto a decrease in thelevels of medianplatelet (273 vs 302; p<0.001) andmedian CRP (0.9 vs 1.3; p<0.001) in allpatientsafterthetreatmentversusbaseline.Inthelight of theresults of ourstudyandtheliterature, we can say thatirondeficiencycauses a chronicinflammatoryprocess.

Keywords: Iron, irondeficiency, inflammation, C-reactive protein

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Özet

Demir, çeşitli hayati biyolojik işlevler için gerekli olan temel bir mineraldir. C-reaktif protein, kronik veya akut inflamasyonun rutin bir belirteci olarak yaygın şekilde kullanılmaktadır. Hem demir eksikliği hem de fazlalığı vücutta proinflamatuar bir duruma neden olur. Demir tedavisi öncesi yüksek olan C-reaktif proteinin, demir tedavisi sonrası düştüğünü klinik olarak gözlemledik. Bu klinik gözlemin gerçekliğini araştırmayı ve sonuçlarımızı literatürle karşılaştırmayı amaçladık.Tek merkezli, prospektif planlanmış bu çalışmaya etik kurul onayı alınarak, 2001 WHO demir eksikliği kriterlerine göre demir eksikliği anemisi saptanan reprodüktif çağda 170 kadın hasta dahil edildi. Hastaların ilk başvuru sırasındaki ve tedaviden 4-8 hafta sonraki hemoglobin, hematokrit, ortalama eritrosit hacmi, lökosit, trombosit, ferritin, folat, C-reaktif protein değerleri kaydedildi. Tüm hastalarda tedavi sonrası tedavi öncesine kıyasla ortalama hemoglobin (11,7±1,4 vs 9,5±1,7; p<0,001), ortalama HCT (36,0±3,6 vs 30,7±4,7; p<0,001), ortalama MCV (76,7±7,8 vs 70,0±9,2; p<0,001) ve ortanca ferritin (43 vs 3,6; p<0,001) düzeylerinde artış saptandı, ortanca platelet (273 vs 302; p<0,001) ve ortanca CRP (0,9 vs 1,3; p<0,001) düzeylerinde düşüş saptandı. Çalışmamızın sonuçları ve literatür bilgileri ışığında demir eksikliğinin kronik inflamatuar bir sürece yol açtığını söyleyebiliriz.

Anahtar Kelimeler: Demir, demireksikliği, inflamasyon, C-reaktif protein

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1. Introduction

Iron is an essential mineral required for a variety of vital biological functions (1). In humans, iron is required for various biochemical processes including cell-mediated immune response in addition to mitochondrial electron transfer reactions, citric acid cycle, gene expression, oxygen binding and transporting, regulation of cellular growth and differentiation (2). Iron excess induces oxidative stress, causing endothelial dysfunction and a chronic inflammation (3, 4). On the other hand, iron deficiency (ID) reduces mitochondrial respiration, respiratory chain complex mechanism, and membrane potential, which may affect the oxidant-antioxidant system. These changes can be regulated by iron treatment (5). ID is a common global public health problem. It is predominantly common among women of reproductive age (6).

ID may cause symptoms both in the presence and absence of anemia, or it may be asymptomatic. Common symptoms and signs include fatigue, drowsiness, reduced concentration, vertigo, tinnitus, paleness, and headache (7). C-reactive protein (CRP) is widely used as a routine marker of chronic or acute inflammation (8).

As iron is a pro-oxidant, it is associated with inflammation and oxidative stress with increased signal pathways. Both iron deficiency and excess induce proinflammatory activity in the body (9, 10).

We clinically observed that CRP, which was high before iron treatment, decreased after iron treatment. We aimed to investigate the authenticity of this clinical observation and compare our results with the literature.

2. Material Method

In this single-center, prospective study, 170 female patients of **reproductive age**, who were admitted to our hospital between July 2020 and February 2021 and found to have iron deficiency anemia (IDA) according to the 2001 WHO iron deficiency criteria (6) and , previously received either iron or iron and B12 combination treatment, were included in this study with the approval of the ethics committee. Patients with HB levels under 12g/dL and ferritin levels under 30 µg/L were considered to have iron deficiency anemia. 85 patients with diagnosed iron deficiency were administered 200 mg/day oral ferrous fumarate, and 85 patients were administered 1000 mg/day, single-dose iv ferric carboxymaltose. Patient follow-up was after 4- 8 weeks after the treatment. Hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), leukocyte (WBC), platelet (PLT), ferritin, folate, c-reactive protein (CRP) values were recorded at the time of first admission and 4-8 weeks after the treatment.

Exclusion criteria

Patients who rejected participating in the study as well as those diagnosed with comorbidities other than ID, malignant diseases, those having developed ID following a gastrointestinal surgery, having an inflammatory gastrointestinal diseases, rheumatic diseases, pregnancy, menopause, amenorrhea, lactating women, those who receive erythrocyte transfusion, patients with acute or chronic infections, those using other medicines other than iron, those who smoke cigarettes, those with hemoglobinopathies, or those who were admitted for follow-up before the first 4 weeks of the treatment or after more than 8 weeks of the treatment were excluded from the study.

Statistical Analysis

Statistical evaluation was performed using Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). Normal distribution of statistical data was evaluated based on Kolmogorov-Smirnov test. Numeric variables with normal distribution were indicated as mean±standard deviation (SD) and numeric variables without normal distribution were indicated as median (i.e., minimum, maximum). Variations in laboratory findings in the entire population and between treatment groups after iron replacement were evaluated by the repeated mixed model analysis. In statistical analyses,

p< 0.05 (*) value was determined to represent statistical significance.

3. Results

Study population consisted of 170 female patients diagnosed with iron deficiency anemia with a mean age of 37.3±9.0 (min.:18; max.:59). Mean age and baseline laboratory findings did not show any significant difference in patients who received oral and IV iron replacement (see Table 1).

Table 1. Distribution of demographic and baseline laboratory findings

Variables	All population	Oral Iron	IV Iron	p
	n=170	**n=85**	**n=85**	
Age, years	37.3±9.0	37.0±9.5	37.6±8.3	0.947
Hemoglobin (g/dL)	9.5±1.7	9.6±1.9	9.4±1.6	0.556
HCT (%)	30.7±4.7	30.9±4.8	30.5±4.5	0.601
MCV (fL)	70.0±9.2	70.8±9.0	69.1±9.3	0.197
WBC (10^3/µı)	6.7±2.0	6.7±1.9	6.8±2.1	0.650
PLT (10^3/µı)	302(131-488)	287(131-488)	312(172-515)	0.961
FERRITIN (µg/L)	3.6(0.5-17.2)	3.7(1.2-17.2)	3.6(0.5-15.7)	0.161
CRP (mg/L)	1.3(0.1-32.1)	1.3(0.1-11.8)	1.2(0.1-32.1)	0.412

Numerical variables were expressed as mean±standard deviation or median (min-max).
** p <0.05 shows statistical significance. WBC: White blood cells, CRP: C-reactive proteins, PLT:Platelets, MCV:Mean corpuscular volume, HCT:Hematocrit*

An increase in the levels of mean hemoglobin (11.7±1.4 vs 9.5±1.7; p<0.001), mean HCT (36.0±3.6 vs 30.7±4.7; p<0.001), mean MCV (76.7±7.8 vs 70.0±9.2; p<0.001), and median ferritin (43 vs 3.6; p<0.001) was observed in addition to a decrease in the levels of median platelet (273 vs 302; p<0.001) and median CRP (0.9 vs 1.3; p<0.001) in all patients after the treatment versus baseline (see Table 2).

Table 2. Change in laboratory findings of IDA patients after treatment

Variables	**Baseline**	**After treatment**	**p**
	n=181	n=181	
Hemoglobin (g/dL)	9.5±1.7	11.7±1.4	<0.001*
HCT (%)	30.7±4.7	36.0±3.6	<0.001*
MCV (fL)	70.0±9.2	76.6±7.8	<0.001*
WBC (10^3/µı)	6.7±2.1	6.9±1.7	0.075
PLT (10^3/µı)	302(131-488)	273(280-552)	<0.001*
Ferritin (µg/L)	3.6(0.5-17.2)	43(2.4-286.3)	<0.001*
CRP (mg/L)	1.3(0.1-32.1)	0.9(0.1-17.8)	<0.001*

Numerical variables were expressed as mean±standard deviation or median (min-max).
** p <0.05 shows statistical significance. WBC: White blood cells, CRP: C-reactive proteins, PLT: Platelets, MCV: Mean corpuscular volume, HCT: Hematocrit*

The effects of age have been adjusted. In patients who were administered IV iron replacement versus those who received oral iron replacement, a higher increase in the

levels of hemoglobin (Δp=0.009), MCV (Δp=0.002), and ferritin (Δp<0.001) were observed after treatment. In both treatment groups, increase in HCT and WBC levels as well as decrease in platelet and CRP levels were similar (see Table 3).

Table 3. Change in laboratory findings after treatment by treatment sub-groups

Variables	Oral Iron Replacement		p	IV Iron Replacement		p	Δp
	Baseline	After treatment		Baseline	After treatment		
	n=181	n=181		n=181	n=181		
HGB (g/dL)	9.6±1.9	11.4±1.5	<0.001*	9.4±1.6	12.0±1.3	<0.001*	0.009*
HCT(%)	30.9±4.8	35.5±3.9	<0.001*	30.5±4.5	36.6±3.2	<0.001*	0.071
MCV(fL)	70.8±9.0	75.8±7.1	<0.001*	69.0±9.3	77.4±8.3	<0.001*	0.002*
WBC(10^3/µı)	6.7±1.9	6.9±1.5	0.095	6.8±2.3	7.0±1.8	0.086	0.318
PLT(10^3/µı)	287(131-488)	274(115-552)	<0.001*	312(172-515)	270(280-520)	<0.001*	0.467
Ferritin (µg/L)	3.7(1.2-17.2)	24.9(2.8-215.6)	<0.001*	3.6(0.5-15.7)	56.1(2.4-286.3)	<0.001*	<0.001*
CRP (mg/L)	1.3(0.1-11.8)	0.9(0-12.6)	<0.001*	1.2(0.1-32.1)	1(0.1-17.8)	<0.001*	0.132

Numerical variables were expressed as mean±standard deviation or median (min-max).
** p <0.05 shows statistical significance.*
Δ = Difference between groups in the amount of change after treatment compared to pretreatment
The effects of age have been adjusted.
HGB: Hemoglobin, WBC: White blood cells, CRP: C-reactive proteins, PLT: Platelets, MCV: Mean corpuscular volume, HCT: Hematocrit

4. Discussion

We compared CRP levels of young women with IDA before and after iron treatment. We found out that CRP levels after iron treatment were lower in both groups compared to those before the treatment. Study results confirmed our clinical observations.

The results from a meta-analysis suggested that iron treatment in patients with cardiac failure could improve cardiac functions in cardiac dysfunction and reduce N-terminal pro b-type natriuretic peptide (NTproBNP), an inflammatory prognostic marker, as well as a reduction in CRP serum levels (11). The results also indicated that the presence of chronic inflammation in cardiac failure was responsible for impaired iron absorption, recycling, and release from iron stores in the body (12). An experiment with lab rats showed that iron deficiency may cause non-apoptotic cell death and inflammation in cultured cells in addition to in-vivo inflammation (13). Fan *et al.* described an increased activation of nuclear factor kappa beta (NF-kB), a proinflammatory transcription factor, in macrophages with iron deficiency (14).

As in iron deficiency, inflammation and endothelial dysfunction also develop in case of iron excess (9,10). For this reason, it is vital to ensure iron balance in the body. The main regulator between iron and inflammation is a peptide called hepcidin (15). Another regulator is hypoxia-inducible factor (HIF) (13). In iron deficiency anemia, inflammation may be induced by both iron deficiency and hypoxia. Hepcidin is an antimicrobial peptide that regulates systemic iron homeostasis. It induces anti-inflammatory response in macrophages. Hepcidin binds to ferroportin, an iron exporter, and causes internalization and impairment of iron by reducing the release of iron from macrophages, duodenal

cells, and hepatocytes (16). Hepcidin production is inhibited in cases of iron deficiency. Experiments proved that hepcidin response to inflammation remained insufficient in case of iron deficiency, causing a proinflammatory activity in case of iron deficiency (15, 17). Both acute and chronic hypoxia are associated with a strong hepcidin suppression (18,19). A decrease in hepcidin after having been exposed to acute hypoxia caused an increase in serum interleukin-6 (IL6) in the absence of any infection or inflammatory condition. After the volunteers have returned to sea level, both IL6 and hepcidin returned to normal levels (19).

In the light of the results of our study and the literature, we can say that iron deficiency causes a chronic inflammatory process. We believe and suggest that comprehensive studies to be designed using high-sensitivity C-reactive protein (hsCRP) before and after iron treatment could contribute to more valuable knowledge to the literature.

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