

Assessing Iron Deficiency Anemia in Obese Adolescents and Identifying Contributing Factors

Obez Ergenlerde Demir Eksikliği Anemisinin Değerlendirilmesi, Rol Oynayan Faktörlerin Belirlenmesi

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ABSTRACT

Objective: Obesity and iron deficiency, which are public health problems that maintain their prevalence and for which the adolescent population is particularly at risk, may have important clinical consequences. This study aimed to assess the iron parameters and blood vitamin B12 levels in obese adolescents and identify the contributing variables to the development of anemia.

Material and Methods: The present study involved a retrospective evaluation of 260 children (130 obese-130 control) who were admitted to the Ankara Children's Haematology Oncology Training and Research Hospital, Pediatric Outpatient Clinics, between March 2013 and May 2015. Children aged 12 to 18 years without acute or chronic illnesses and body mass index (BMI) above the 95th percentile for age and gender were required for inclusion in the study group. Data from patient files were used to collect information on physical examination findings, sociodemographic characteristics, daily dietary status, and level of physical activity. All patients had evaluations for CRP, iron parameters, vitamin B12, and complete blood count.

Results: The study revealed that the obese group had significantly higher serum ferritin levels ($p=0.002$) and lower serum iron and vitamin B12 levels ($p=0.036$ and 0.047 , respectively) as compared to the control group. In the obese population, elevated BMI has been demonstrated to be correlated with elevated CRP and ferritin levels.

Conclusion: Obesity's chronic inflammation state may lead inflammatory pathophysiological pathways to activate resulting in iron deficiency and other nutritional deficiencies. Obesity should be followed up as a chronic disease and monitored in terms of nutritional deficiencies, especially in adolescents who have not completed their growth.

Key Words: Adolescence, Iron deficiency, Obesity

ÖZ

Amaç: Ergen nüfusun özellikle risk altında olduğu, yaygınlığını koruyan halk sağlığı sorunlarından obezite ve demir eksikliğinin önemli klinik sonuçları olabilmektedir. Bu çalışmada obez ergenlerde demir parametrelerinin ve serum vitamin B12 düzeylerinin değerlendirilmesi ve anemi gelişiminde rol oynayan faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada T.C. Sağlık Bakanlığı Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Polikliniklerine Mart 2013-Mayıs 2015 tarihleri arasında başvuran 260 çocuk (130 obez, 130 kontrol) geriye dönük olarak değerlendirilmiştir. Akut veya kronik hastalığı olmayan ve vücut kitle indeksi (VKİ)



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Conflict of Interest / Çıkar Çatışması: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / Etik Kurul Onayı: This study was conducted in accordance with the Helsinki Declaration Principles. The study received Ethics Committee approval from Ankara Child Health and Diseases Hematology Oncology Hospital (2017-096/ 03.07.2017).

Contribution of the Authors / Yazarların katkısı: **KILINÇ Ş:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **ÖDEN AKMAN A:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. **ŞAYLI TR:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / Atıf yazım şekli : Kılınç Ş, Öden Akman A and Şaylı TR. Assessing Iron Deficiency Anemia in Obese Adolescents and Identifying Contributing Factors. Turkish J Pediatr Dis 2024;18:186-191.

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Received / Geliş tarihi : 08.01.2024

Accepted / Kabul tarihi : 06.03.2024

Online published : 02.05.2024

Elektronik yayın tarihi

DOI: 10.12956/tchd.1416473

yaş ve cinsiyete göre 95. persentilin üzerinde olan 12-18 yaş arası çocuklar çalışma grubuna dahil edilmiştir. Fiziksel muayene bulguları, sosyodemografik özellikler, günlük beslenme durumu ve fiziksel aktivite düzeyi hakkında bilgi toplamak için hasta dosyalarından elde edilen veriler kullanılmıştır. Tüm hastalarda CRP, demir parametreleri, B12 vitamini ve tam kan sayımı değerlendirilmeleri yapılmıştır.

Bulgular: Serum demir ve vitamin B12 düzeyleri, obez grupta kontrol gruba oranla düşük (sırasıyla $p = 0.036$, $p = 0.047$), serum ferritin düzeyi ise obez grupta kontrol gruba kıyasla istatistiksel olarak anlamlı derecede yüksek saptanmıştır ($p=0.002$). Obez grupta yüksek CRP düzeylerinin, artmış VKI ile ilişkili olduğu gösterilmiştir.

Sonuç: Obezitenin kronik enflamasyon durumu, enflamatuvar patofizyolojik yolların aktive olmasına neden olarak demir eksikliği ve diğer beslenme yetersizliklerine yol açabilir. Obezite kronik bir hastalık olarak takip edilmeli ve özellikle büyümesini tamamlamamış ergenlerde beslenme yetersizlikleri açısından izlenmelidir.

Anahtar Sözcükler: Ergenlik dönemi, Demir eksikliği, Obezite

INTRODUCTION

Over 650 million people and 340 million children suffer from obesity, an energy metabolism condition that can cause both physical and psychological issues (1, 2). Different population segments have varying prevalence rates. Compared to children aged 2–5, this rate is higher in children aged 6–11 and 12–19 (3). According to the World Health Organization (WHO), obesity presents a serious risk to public health and is classified as a chronic illness.

Children and adolescents with obesity appear to have a paradoxical malnutrition in terms of their nutritional condition. Micronutrient deficits are prevalent even with high dietary consumption rates (4). Apart from increasing the risk of diabetes mellitus, cancer, and cardiovascular disease, obesity has also been connected to iron deficiency anemia (IDA), which is another issue related to general public health (2, 5). According to the WHO, globally, anemia affects 1.62 billion people, which corresponds to 24.8% of the population. Iron deficiency (ID) with or without anemia may lead to a broad spectrum of signs and symptoms. Even if iron deficiency in adolescents is not severe enough to cause anemia, it can nevertheless induce cognitive and physical problems. Adolescence is considered a period of increased risk of ID due to accelerated growth, rise of blood volume, menstrual blood loss in girls, greater muscle mass in boys, and unbalanced diets (6).

Growing evidence supports the existence of an association between obesity and ID. This link was observed among children, adolescents, and adults. The low-grade systemic inflammation that is present in obese people is the primary mechanism that connects obesity and ID (7). Interleukin-6 and serum hepcidin levels were considerably higher in overweight and obese people than in people of normal weight. Pro-inflammatory cytokines like interleukin-6 enhance the liver's hepcidin production. According to a recent study, even with iron-rich diets, overweight and obese women with central adiposity had greater blood hepcidin, lower iron levels, and reduced iron absorption (8). Even so, some research has determined the higher risk of vitamin and mineral deficiencies in malnourished children with obesity, overweight, and metabolic syndrome. Therefore, it was thought

that inadequate dietary composition, brief, frequently restricted diets, or higher requirements could be the cause of the drop in serum vitamin B12 levels (9). A study revealed that among Mexican children aged 8 to 15, the relationship between serum concentrations of vitamin B12 and Body Mass Index (BMI) was inverse (10).

This study aims to assess the iron parameters and blood vitamin B12 levels in obese adolescents and identify the contributing variables to the development of anemia.

MATERIAL and METHODS

The present study involved a retrospective evaluation of 260 children (130 obese and 130 control) who were admitted to the Ankara Children's Haematology Oncology Training and Research Hospital, Pediatric Outpatient Clinics of the Ministry of Health, between March 2013 and May 2015. Patients with BMIs above the age and gender-specific 95th percentile, between the ages of 12 and 18 years, without known acute or chronic illnesses, and admitted to our hospital due to obesity were included. The control group consisted of individuals with a BMI between the 5 and 95 percentile and no acute or chronic illnesses.

The results of the physical examination, body weight, height, BMI, waist circumference, family history, socioeconomic factors, physical activity levels, daily diet, and menarche status in girls were all documented along with the evaluation of the patient files. The BMI percentile values developed by Bundak and colleagues (11) were applied to evaluate obesity. The metabolic equivalent task score (MET) was used to calculate the levels of physical activity (12). The daily intake of iron was categorized as being below or above 10 mg based on the quantity and composition of nutrients (13). The three socioeconomic levels are those with a wage below the minimum (1st level), those with a wage greater than twice the minimum (3rd level), and those in between (2nd level).

All patients had their levels of ferritin, vitamin B12, serum iron (SI), total iron binding capacity (TIBC), C-reactive protein (CRP), and complete blood count assessed. The obese group also

Table I: Grouping patients based on hematological characteristics

	Hb	MCV	SI	Ferritin
Iron deficiency	N	N	↓	↓
Iron deficiency anemia	↓	↓	↓	↓

had evaluations of liver function tests, triglycerides, cholesterol, fasting blood glucose, and fasting insulin levels. For girls and boys, respectively, the lower limit of hemoglobin (Hb) values was determined to be 12 g/dl and 13 g/dl. Red cell distribution width (RDW) values in the range of 11.5%–14.5% were regarded as normal, and the lower limit of the mean corpuscular volume (MCV) value was accepted as 78 fL (14). As indicated in Table I, patients were categorized based on hematological characteristics.

The statistical analysis was carried out using the SPSS for Windows 22.0 (IBM Corp., Armonk, NY, USA) package. The descriptive statistics were displayed as the number of cases (n) and percentage (%) for categorical variables, as the mean \pm standard deviation (SD) and median/interquartile range (IQR) for continuous and discrete numerical variables. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. For normally distributed values, the Student's t-test demonstrated the significance of the group difference; for non-normally distributed and ordinal variables, the Mann-Whitney U test was used. The chi-square test was used for comparisons of categorical data. Ferritin, BMI, and CRP levels have been linked using the Spearman correlation test. The significance threshold was set at 0.05, and a significant relationship between the groups was acknowledged when $p < 0.050$.

RESULTS

The control group had an average age of 14.68 ± 1.52 years, whereas the obese group had an average age of 14.07 ± 1.65 years. There was no statistically significant difference in the gender and mean age distributions between the groups ($p = 0.606$ and $p = 0.266$, respectively). Regarding the menarche status, duration of menarche, hypermenorrhea in females, birth weight, and breastfeeding in all children, there was no difference between the control and obese groups. Monthly income level 1 was lower in the obese group (3.8%) compared to the control group (13.1%), while monthly income level 3 was significantly higher in the obese group (46.9%) compared to the control group (34.6%). The groups' sociodemographic information is shown in Table II.

The control and obese groups did not differ statistically significantly in terms of daily iron intake or level of physical activity. The prevalence of diabetes, cardiovascular disease,

Table II: Demographic data for each group

	Control group*	Obese group*	p
Birth weight			
< 2500 g	8 (6.3)	11 (8.5)	0.508
\geq 2500 g	118 (93.7)	118 (91.5)	
Breastfeeding			
< 1 year	59 (46.8)	63 (48.8)	0.748
\geq 1 year	67 (53.2)	66 (51.2)	
Menarche status			
(-)	11 (12.9)	12 (14.8)	0.727
(+)	74 (87.1)	69 (85.2)	
Menarche duration			
< 1 year	7 (9.5)	12 (17.4)	0.163
\geq 1 year	67 (90.5)	57 (82.6)	
Hypermenorrhea			
(-)	64 (86.5)	59 (85.5)	0.866
(+)	10 (13.5)	10 (14.5)	
Socioeconomic status			
1 st level	17 (13.1)	5 (3.8)	0.011
2 nd level	68 (52.3)	64 (49.2)	
3 rd level	45 (34.6)	61 (46.9)	

*n (%), Chi-square Test. $p < 0.050$ is significant.

Table III: Hb, RBC, MCV, RDW, SI, TIBC, ferritin and vitamin B12 levels

	Control group	Obese group	p
Hb (g/dL)*	13.79 ± 1.33	13.72 ± 1.18	0.616
RBC ($10^6/\mu\text{L}$)*	4.89 ± 0.43	4.97 ± 0.41	0.137
MCV (fL)*	82.73 ± 6.18	81.79 ± 5.20	0.187
TIBC (ng/mL)*	367.12 ± 65.77	365.71 ± 64.03	0.862
RDW (%)*	13.8 /13.1-14.95	13.9 /13.3-14.62	0.765
SI ($\mu\text{g/dL}$)*	67 /46.5-105.5	65.5 /43-86	0.036
Ferritin(ng/mL)*	17.6 /8.1-30-95	24.7 /14.95-36	0.002
Vit B12 (pg/mL)*	202 /157.25-254	186.5 /136.75-245.75	0.047

*:mean \pm SD(standard deviation), †: median / IQR (Interquartil Range). The Student's t-Test, Mann Whitney U Test. $p < 0.050$ is significant.

and obesity in the family was shown to be greater in the obese group ($p < 0.001$, $p = 0.033$, and $p < 0.001$, respectively). The groups did not differ in terms of how much milk, eggs, cheese, red meat, vegetables, or oranges they consumed daily when asked about their nutritional condition ($p = 0.620$, $p = 0.119$, $p = 0.281$, $p = 0.123$, $p = 0.483$, and $p = 0.500$, respectively).

The study revealed that the obese group had significantly higher serum ferritin levels ($p = 0.002$) and lower SI and vitamin B12 levels ($p = 0.036$ and 0.047 , respectively) as compared to the control group (Table III). Compared to the control group ($n = 58$), there were fewer patients in the obese group ($n = 32$) with low blood ferritin levels ($p = 0.001$). Regarding IDA (low Hb, MCV, SD, and ferritin combined), there was no statistical difference between the groups ($p = 0.349$).

Patients with daily iron intake > 10 mg had statistically substantially higher levels of Hb and ferritin than those with daily

Table IV: The relationship between daily iron intake and Hb, RBC, MCV, RDW, TS, TIBC, vitamin B12, SI, and ferritin levels in the groups

Daily iron intake	Control group	Obese group	p*	p†
Hb (g/dL)‡				
<10 mg	13.46±1.23	13.60±1.24	0.001	0.176
>10 mg	14.23±1.35	13.89±1.10		
RBC (10 ⁶ /μL)‡				
<10 mg	4.84±0.43	4.93±0.42	0.076	0.106
>10 mg	4.98±0.45	5.05±0.42		
MCV (fL)‡				
<10 mg	81.88±6.98	81.85±5.10	0.074	0.913
>10 mg	83.84±4.86	81.75±5.40		
TIBC (ng/mL)‡				
<10 mg	373.43±67.39	366.05±61.26	0.222	0.944
>10 mg	359.14±63.37	365.25±68.11		
RDW (%)§				
<10 mg	13.95 /13.12-15.45	13.95 /13.2-14.5	0.073	0.803
>10 mg	13.6 /13-14.35	13.85 /13.4-14.95		
Vit B12 (pg/mL)§				
<10 mg	197 /144-254	180.5 /129.75-230.5	0.698	0.280
>10 mg	203 /175-254	190.5 /144.5-277		
SI (μg/dL)§				
<10 mg	65 /40.25-99	65 /42.75-79.75	0.094	0.478
>10 mg	73/ 54.5-115.5	67.5 /44.5-91.25		
Ferritin (ng/mL)§				
<10 mg	14.15 /6.52-29.27	26 /13.82-37.25	0.015	0.959
>10 mg	23.1/13.45-31.9	24.55 /16-35.3		

*: Control group, †: Obese group, ‡: mean ±SD (Standard Deviation), §: median / IQR (Interquartil Range). The Student's t-Test, Mann Whitney U Test. p<0.050 is significant.

Table V: Hb, RBC, MCV, RDW, TS, TIBC, vitamin B12, SI, and ferritin levels with BMI in all patients

	BMI (kg/m ²)	
	p	r
Hb (g/dL)	0.625	0.031
RBC (10 ⁶ /μL)	0.017	0.148
MCV (fL)	0.207	-0.079
RDW (%)	0.683	0.026
TS (%)	0.078	-0.110
TIBC (ng/mL)	0.587	-0.034
Vit B12 (pg/mL)	0.073	-0.112
SI (μg/dL)	0.207	-0.079
Ferritin (ng/mL)	0.001	0.200

Spearman Test. p<0.05 is significant.

iron intake <10 mg in the control group (p = 0.001; p = 0.015) (Table IV).

Table V illustrates a positive correlation between BMI and the levels of ferritin (p=0.001; r=0.200) and RBC (p=0.017; r=0.148). Figure 1 shows for every unit increase of 1 kg/m² in BMI, the ferritin levels increased by 0.562 ng/mL.

In the obese group, Table VI presents the correlation between elevated CRP levels and elevated BMI (p = 0.024; r = 0.199). In the obese group, RDW levels rose in parallel with rising CRP levels (p = 0.039; r = 0.181).

Table VI: The correlation between ferritin levels, vitamin B12, SI, BMI, Hb, RBC, MCV, RDW, TS, TIBC and CRP in the obese group

	CRP (mg/dL)	
	p	r
BMI (kg/m ²)	0.024	0.199
Hb (g/dL)	0.153	0.126
RBC (10 ⁶ /μL)	0.845	0.017
MCV (fL)	0.112	-0.140
RDW (%)	0.039	0.181
TS (%)	0.141	-0.130
TIBC (ng/mL)	0.255	-0.101
Vit B12 (pg/mL)	0.451	0.067
SI (μg/dL)	0.055	-0.169
Ferritin (ng/mL)	0.077	0.156

Spearman Test. p<0.050 is significant.

DISCUSSION

Clinical outcomes can be significant for obesity and ID, two public health issues that continue to be prevalent and for which adolescents are especially vulnerable (15). Obesity prevalence is currently 16%–31%, and it has dramatically increased in recent years (16). The inverse association between iron and obesity has been described in both adults and children, but it is not currently sufficiently clarified. Many studies demonstrated

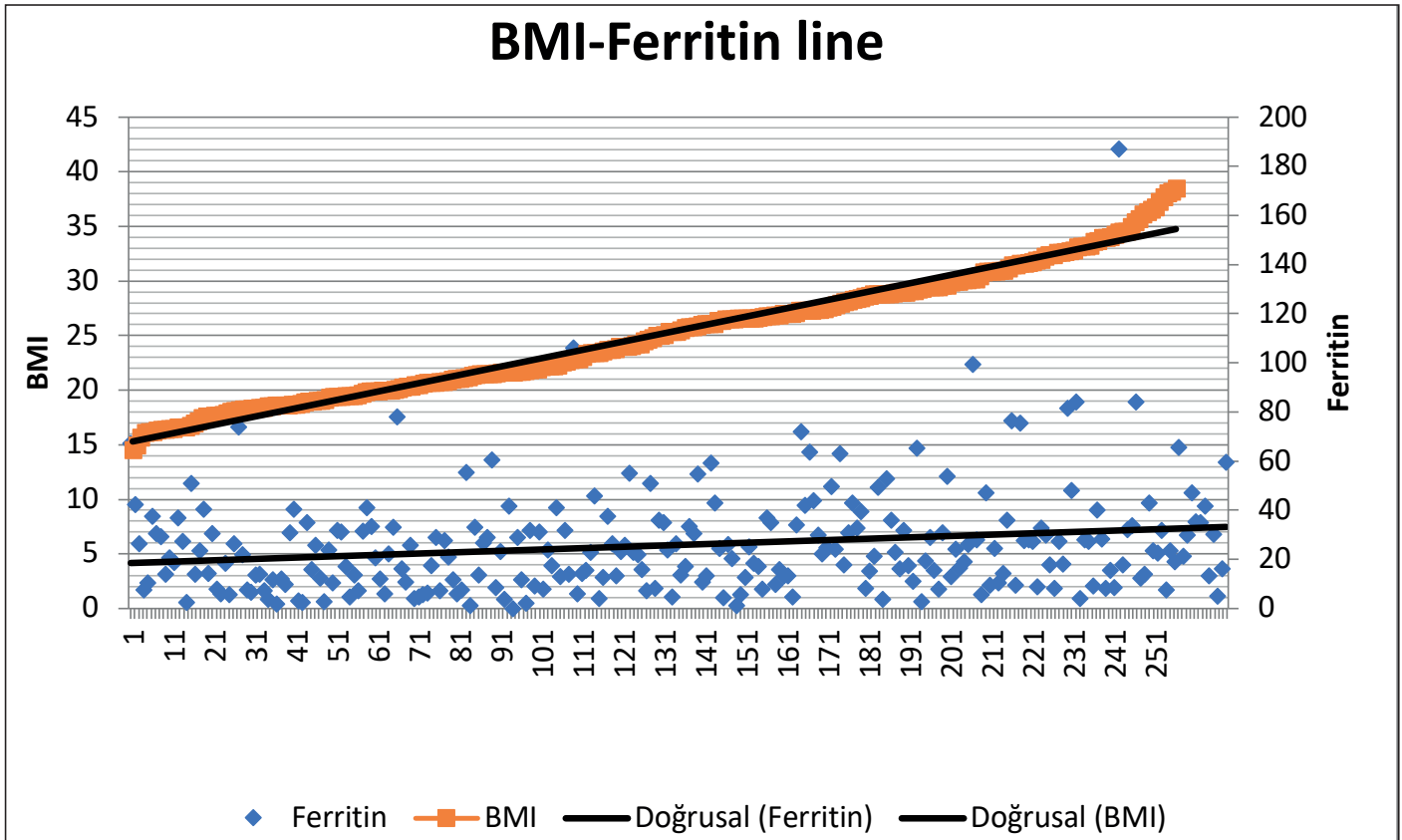


Figure 1: BMI-Ferritin

an increased risk of ID in line with the BMI. This relationship could be explained by: 1) an increase in iron requirements, due to the greater blood volume required by the increased body weight, provoking a real ID; 2) a decrease in the bioavailability of iron due to its sequestration in the reticuloendothelial system (assuming that obesity is a chronic inflammatory state, which would imply functional ID); and 3) both situations. Current evidence identifies hepcidin, a hormonal peptide secreted by the liver and the adipocytes, as a major factor in the alteration of iron metabolism that is observed in subjects with obesity. The proinflammatory cytokines that are characteristic of obesity would induce an increase in the production of hepcidin, thus reducing the absorption of iron in the intestine and its release from the macrophages (causing functional ID from decreased iron delivery for erythropoiesis), and an increase in the synthesis of ferritin in the reticuloendothelial cells (15). Other factors that could account for iron insufficiency in obese children include a diet rich in calories, a diet low in iron, a sedentary lifestyle that reduces myoglobin dissolution, and an increased need for iron because of larger red blood cells (17).

There is evidence that ID, whose risk increases in adolescence, impacts neurocognitive outcomes. Therefore, it may be essential to work to reduce health disparities among populations that are at risk during this critical period (18). A study revealed that the 12–16 age group was more likely to suffer from iron insufficiency and IDA (19).

According to a Chilean study, children from low socioeconomic properties were far more likely than those from high socioeconomic families to be overweight or obese (20). A study performed in our country revealed the high-income group had greater rates of obesity (21). Similarly, we found the obese group had a higher income level in our study. As reported in the literature, our study's findings indicated that the obese group also had higher incidences of diabetes, cardiovascular disease, and obesity in their families (22).

Obesity has been reported to be associated with ID frequently (19). Serum iron levels in the obese group in our study were lower than those in the control group, but there was no difference in IDA. The inadequate daily intake of iron in the majority of children in both groups and the lack of variation in consumption between the groups disproved the theory that the low serum iron level in the obese group was caused by low daily iron intake. Hb and ferritin levels were found to be statistically significantly higher in the control group with daily iron intake >10 mg compared to those with daily iron intake <10 mg, highlighting the significance of nutrition in healthy children, even though no correlation was found between daily iron intake and Hb and ferritin levels in the obese group.

Ferritin is an acute-phase protein that is upregulated during infections, inflammatory states, and malignant diseases. It is suggested that serum ferritin level is elevated in response to inflammation in obesity, even in persons with ID (17). Ferritin

levels were found to be higher in the obese group in our study than in the control group ($p=0.002$). Ferritin level and BMI were found to be significantly positively correlated. The ferritin levels increased by 0.56 ng/mL for every 1 kg/m² increase in BMI, according to the results of a linear regression analysis. The fact that the rate of anemia in our study's obese patients was the same as that of the control group suggests that the patients' high ferritin and low SI levels could be more consistent with chronic inflammation than with chronic infection anemia. In our research, we found that elevated BMI in obese patients was correlated with elevated CRP levels. However, the interpretation of chronic inflammation anemia is limited because the inflammatory indices hs-CRP, TNF- α , IL-6, and hepcidin could not be assessed.

The principal mechanism that links obesity and iron deficiency is low-grade systemic inflammation. Obesity's chronic inflammation state may lead inflammatory pathophysiological pathways to activate resulting in iron deficiency and other nutritional deficiencies. Obesity should be followed up as a chronic disease and monitored in terms of nutritional deficiencies, especially in adolescents who have not completed their growth.

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