

The relationship between iron and lipid metabolism in overweight and obese children

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ABSTRACT

Objective: Obesity is a chronic inflammatory disease characterized by an increase in body fat mass resulting from a disturbed energy balance. It is an independent risk factor for cardiovascular diseases. Obesity-related chronic inflammation has been shown to negatively affect lipid balance through iron metabolism. The aim of this study was to investigate the effect of chronic inflammation on iron and lipid metabolism in overweight and obese children and to determine the relationship between them.

Material and Methods: This prospective case-control study included fifty-one overweight, sixty-one obese, and fifty healthy controls aged twelve to eighteen years. Lipid profile, iron parameters, and high-sensitivity C-reactive protein levels were analyzed, and the relationships between the groups were determined.

Results: The obese group had lower serum iron and iron/hepcidin ratio and higher total iron-binding capacity values compared to the other groups. There was no difference between the groups in hepcidin and soluble transferrin receptor levels. High-sensitivity C-reactive protein levels were higher in the obese and overweight groups compared to the control group. There was a positive correlation between hepcidin and total cholesterol and low-density lipoprotein, and a negative correlation between iron and high-density lipoprotein in the obese group.

Conclusion: Serum iron levels were lower in obese children compared to controls, which was attributed to chronic inflammation rather than iron deficiency. It may be concluded that chronic inflammation in childhood obesity does not increase hepcidin levels and thus does not adversely affect lipid metabolism.

Keywords: Child; dyslipidemia; hepcidin; iron; obesity.

Cite this article as: Dervişoğlu Çavdaroglu P, Kaya Ünlü D. The relationship between iron and lipid metabolism in overweight and obese children. Jour Umraniye Pediatr 2025;5(2):59–64.

Received (Başvuru): 02.07.2025 **Revised (Revizyon):** 28.08.2025 **Accepted (Kabul):** 01.09.2025 **Online (Online yayınlanma):** 30.10.2025

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Fazla kilolu ve obez çocuklarda demir ve lipid metabolizması arasındaki ilişki

ÖZET

Amaç: Obezite, enerji dengesinin bozulması sonucu vücut yağ kütlelerinde artış ile karakterize kronik inflamatuvar bir hastalıktır. Kardiyovasküler hastalıklar için bağımsız bir risk faktörüdür. Obeziteyle ilişkili kronik inflamasyonun demir metabolizması yoluyla lipid dengesini olumsuz etkilediği gösterilmiştir. Bu çalışmanın amacı, fazla kilolu ve obez çocuklarda kronik inflamasyonun demir ve lipid metabolizması üzerindeki etkisini araştırmak ve aralarındaki ilişkiyi belirlemektir.

Gereç ve Yöntemler: Çalışmamız prospektif bir vaka-kontrol çalışmasıdır. Çalışmaya on iki-on sekiz yaş arası elli bir fazla kilolu, altmış bir obez ve elli sağlıklı kontrol dahil edildi. Lipid profili, demir parametreleri ve yüksek duyarlılıklı C-reaktif protein düzeyleri analiz edildi ve gruplar arasındaki ilişkiler belirlendi.

Bulgular: Obez grupta, diğer gruplara kıyasla daha düşük serum demiri ve demir/hepsidin oranı ile daha yüksek total demir bağlama kapasitesi değerleri bulundu. Hepsidin ve solubl transferrin reseptör düzeyleri açısından gruplar arasında fark yoktu. Yüksek duyarlılıklı C-reaktif protein düzeyleri obez ve fazla kilolu gruplarda kontrol grubuna göre daha yüksek bulundu. Obez grupta hepsidin ile total kolesterol ve düşük dansiteli lipoprotein arasında pozitif; demir ile yüksek dansiteli lipoprotein arasında negatif korelasyon saptandı.

Tartışma: Obez çocuklarda serum demir düzeyleri kontrollere kıyasla daha düşüktü; bu durum demir eksikliğinden ziyade kronik inflamasyona bağlandı. Çocukluk çağı obezitesinde kronik inflamasyonun hepsidin düzeylerini artırmadığı ve dolayısıyla lipid metabolizmasını olumsuz etkilemediği sonucuna varılabilir.

Anahtar Kelimeler: Çocuk; demir; dislipidemi; hepsidin; obezite.

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INTRODUCTION

Childhood obesity is a chronic inflammatory disease with an increasing prevalence. The decreasing trend in the age of onset has also increased the frequency of obesity-related complications. Obesity is a risk factor for the development of cardiovascular disease, and comorbidities such as dyslipidemia further increase this risk (1). There are studies on the risk of developing cardiovascular disease due to chronic inflammation in obese children, and there are also studies showing that this chronic inflammation may adversely affect lipid balance through iron metabolism (2, 3). In our study, we aimed to determine the effect of obesity-related chronic inflammation on iron and lipid metabolism and the relationship between them in children.

MATERIAL AND METHODS

Our study is a prospective case-control study. Ethics committee approval was obtained from the ethics committee of a university (no: E.16214662-050.01.04-1732306). The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 162 children aged 12–18 years participated in the study. The study included 51 patients who were evaluated as overweight between the 85th–95th percentiles according to body mass index (BMI), 61 patients who were evaluated

as obese above the 95th percentile according to BMI, and 50 healthy children with BMI between the 5th–85th percentiles.

Children with obesity due to secondary or genetic causes, a history of early cardiovascular disease, chronic diseases, long-term medication use for any reason, infections with high fever within the last 15 days, and smokers were not included in the study. The control group consisted of patients presenting for medical reports, preoperative evaluations before minor surgical procedures, or routine pediatric health examinations. Systemic examinations, height, body weight, and blood pressure measurements were performed by the same physician.

Venous blood samples were collected in the morning after 12 hours of fasting. According to the measured blood lipid parameters, participants in the obese and overweight groups with one or more of the following reference values—high-density lipoprotein (HDL) <40 mg/dL, total cholesterol (TC) ≥200 mg/dL, low-density lipoprotein (LDL) ≥130 mg/dL, and triglyceride (TG) ≥130 mg/dL—were considered dyslipidemic.

Statistical Analysis

Statistical analyses were performed using IBM SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA). For descriptive statistics, numbers and percentages were used for categorical variables; mean and standard deviation were used for numerical variables with normal distribution; and median and minimum–maximum

Table 1. Comparison of demographic and anthropometric data between groups

	Control (n=50)	Owerweight (n=51)	Obese (n=61)	p
Gender n (%)				
Female	25 (50%)	30 (59%)	38 (62%)	0.417
Male	25 (50%)	21 (41%)	23 (38%)	
Age (year)	14.7±4.04	13.86±1.65	14.34±1.7	0.072
Weight (kg)	53 (35–80)	64 (43–86) ^a	86 (52–126) ^{b, c}	<0.001
Height (cm)	162 (138–186)	160 (135–177)	162.9 (138–182)	0.147
BMI	19.3 (12.4–24.8)	24.9 (21.7–28.4) ^a	32.3 (25.5–43.8) ^{b, c}	<0.001
BMI percentile	42.1 (3.7–84)	92 (85.1–94.9) ^a	99.2 (94.5–99.9) ^{b, c}	<0.001

Kruskal-Wallis test was used to compare the groups (intra-group comparisons were made with Mann-Whitney U test) and the data were given as mean±standard deviation and median (min–max). Age was compared using Kruskal-Wallis test and gender was compared using Chi-Square test. a: Control and overweight group compared; b: Overweight and obese group compared; c: Control and obese group compared; BMI: Body mass index.

Table 2. Comparison of hsCRP and iron parameters between groups

	Control (n=50) Median (Min-Max)	Owerweight (n=51) Median (Min-Max)	Obese (n=61) Median (Min-Max)	p
HGB (g/dL)	12.8 (11.3–17.1)	12.7 (10.1–16.0)	13 (10.4–15.2)	0.274
MCV (fl)	86.7 (75.7–98.0)	85.3 (69.5–93.7)	85.3 (67.1–105.0)	0.13
hsCRP (ng/mL)	0.2 (0.0–8.8)	0.8 (0.1–8.3) ^a	1.3 (0.1–17.4) ^{b, c}	<0.001
Iron (µg/L)	88 (18–199)	77 (13–166)	62 (21–149) ^c	0.003
TIBC (µg/L)	368.5 (128–528)	393 (129–533)	408.5 (183–515) ^c	0.014
Tf (g/L)	2.6 (1.6–3.8)	2.8 (0.01–4.4)	2.64 (2.13–3.85)	0.093
Ferritin (µg/L)	32.3 (6.1–81.5)	25.4 (1.4–128)	23.0 (1.0–98.5)	0.114
Hepsidin (µg/L)	30.4 (17.4–74.1)	31.2 (9.8–51.0)	31.8 (8.6–496.5)	0.667
sTfR (pg/ml)	375.4 (236.9–1632)	363.6 (116.6–629.4)	355.7 (217.7–1586)	0.136
Iron/ferritin	2.79 (0.27–18.16)	3.09 (0.29–21.11)	2.93 (0.0–38.89)	0.634
Iron/hepsidin	2.82 (0.24–6.44)	2.5 (0.55–8.45)	1.75 (0.0–10.23) ^{b, c}	0.002

Kruskal Wallis and Mann-Whitney U test were used to compare the groups. a: Control and overweight group compared; b: Overweight and obese group compared; c: Control and obese group compared; HGB: Hemoglobin; MCV: Mean corpuscular volume; hsCRP: High-sensitivity C-reactive protein; TIBC: Total iron-binding capacity; Tf: Transferrin; sTfR: Soluble transferrin receptor; Min: Minimum; Max: Maximum.

values were used for those without normal distribution. For comparisons of numerical variables in independent groups, the Student's t-test was used for two-group comparisons when the normality assumption was met, and one-way ANOVA with post-hoc Tukey test for three or more groups. When normal distribution was not met, Kruskal–Wallis and Mann–Whitney U tests were used. Comparisons of proportions in independent groups were performed using the Chi-square or Fisher's exact Chi-square test. Spearman's rank correlation analysis was used to determine correlations between continuous numerical variables, and linear regression analysis was used to assess linear relationships. In all analyses, $p < 0.05$ was accepted as the level of statistical significance.

RESULTS

In this study, the mean BMI of obese children was 32.3 kg/m², the mean BMI of overweight children was 24.9 kg/m², and the mean BMI of the control group was 19.3 kg/m². The demographic characteristics and anthropometric measurements of the groups are presented in Table 1. High-sensitivity C-reactive protein (hsCRP), iron, and lipid parameters were analyzed according to the groups. The hsCRP level was found to be higher in the overweight group compared to the control group ($p < 0.05$), while iron and HDL-C parameters were lower in the obese group compared to the control group ($p < 0.05$). In the obese group, hsCRP, TIBC, LDL-C,

Table 3. Comparison of lipid parameters between groups

	Control	Owerweight	Obese	p
HDL-C (mg/dL)	50 (35–70)	50 (31.2–78)	43 (31–101) ^{b, c}	<0.001
LDL-C (mg/dL)	94.0±23.0	100.1±23.8	108.2±22.6 ^c	0.007
TK (mg/dL)	157.7±28.6	166.3±29.55	168.0±28.2	0.152
TG (mg/dL)	74 (29–253)	81 (38–256)	108 (48–308) ^{b, c}	<0.001

Group-1: Control group; Group-2: Overweight group; Group-3: Obese group, When One Way ANOVA (Analysis of variance) and *post hoc* tukey test were used to compare the groups, the data were given as mean±standard deviation; when Kruskal Wallis and Mann-Whitney U test were used, the data were given as median (min–max) a when Group-1 was compared with Group-2, b when Group-2 was compared with Group-3, c when Group-1 was compared with Group-3. HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TK: Total cholesterol; TG: Triglyceride; p: Probability value.

Table 4. Correlation analysis between lipid parameters and hsCRP and iron parameters in obese group

	HGB	MCV	Iron	TIBC	Tf	Ferritin	Hepcidin	sTfR	Iron/ ferritin	Iron/ hepcidin
HDL-C										
r	-0.129	-0.18	-0.258*	-0.04	-0	-0.095	0.045	0.091	-0.026	-0.236
p	0.327	0.17	0.049	0.743	0.985	0.472	0.732	0.488	0.843	0.069
LDL-C										
r	0.1	0.043	0.066	-0.1	0.113	0.215	0.330*	-0.13	-0.155	-0.145
p	0.445	0.741	0.62	0.456	0.4	0.102	0.01	0.336	0.242	0.269
TC										
r	0.009	-0.02	-0.016	-0.09	0.114	0.201	0.303*	-0.14	-0.173	-0.19
p	0.947	0.867	0.904	0.481	0.393	0.127	0.019	0.282	0.191	0.146
TG										
r	0.142	-0.1	0.128	0.242	0.057	0.245	0.023	-0.2	-0.148	0.044
p	0.278	0.446	0.333	0.067	0.671	0.062	0.859	0.122	0.263	0.736
hsCRP										
r	-0.192	-0.13	-0.349**	0.017	-0.16	-0.101	0.166	-0.14	-0.065	-0.357**
p	0.138	0.325	0.007	0.897	0.222	0.442	0.2	0.278	0.621	0.005

Spearman correlation analysis was performed. HGB: Hemoglobin; MCV: Mean corpuscular volume; TIBC: Total iron-binding capacity; Tf: Transferrin, sTfR: Soluble transferrin receptor; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; hsCRP: High-sensitivity C-reactive protein; r: Correlation coefficient; p: Probability value.

Table 5. Multiple linear regression analysis results of independent variables affecting hepcidin in obese group

	Coefficients β	p	95.0% CI
HDL-C	0.077	0.730	-1.717–2.440
LDL-C	0.312	0.502	-1.493–3.025
TC	-0.215	0.665	-2.439–1.564
TG	0.211	0.144	-0.067–0.455

CI: Confidence interval; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

and TG levels were significantly higher than in the control group ($p<0.05$). When overweight and obese patients were compared, hsCRP and TG levels were higher, and HDL-C levels were lower in the obese group ($p<0.05$).

In our study, dyslipidemia was found in 40% of the obese group and 25% of the overweight group. No differences were found between the groups in hemoglobin (HGB), mean cell volume (MCV), transferrin (Tf), ferritin, total cholesterol (TC), hepcidin and soluble transferrin receptor (sTfR) levels ($p>0.05$). The iron/hepcidin ratio was significantly lower in the obese group compared to the control and overweight groups ($p<0.05$). Comparisons of hsCRP, iron, and lipid parameters between the groups are shown in Tables 2 and 3.

In the obese group, there was a negative correlation between serum iron and HDL cholesterol and a positive correlation between hepcidin and LDL cholesterol and TC; however, no significant relationship was found in linear regression analysis (Table 4, 5).

DISCUSSION

There are studies showing that overweight and obese children have a higher risk of iron deficiency than those with normal body weight (4, 5). In our study, serum iron was found to be lower and TIBC values higher in the obese group compared to the control, in accordance with the literature. Adipose tissue causes chronic low-grade inflammation through adipocytokines and predisposes individuals to the development of metabolic complications associated with obesity (6). Adipocytokines cause metabolic complications by affecting glucose and lipid balance, while free fatty acids secreted from increased adipose tissue impair insulin sensitivity and constitute an important link between atherosclerotic vascular diseases (7).

As a new perspective on the mechanisms of dyslipidemia development, which have been explained by increased synthesis of fatty acids from adipose tissue and inflammation, we also investigated iron load in macrophages and inflammation-related changes in lipid metabolism in our study. Among the groups, hsCRP values were higher in the obese group compared to the control and overweight groups, and higher in the overweight group compared to the control. No differences were found between the groups in HGB, Tf, ferritin, hepcidin, and sTfR values. These results support that obesity leads to chronic inflammation and lowers serum iron levels. Although serum iron levels decreased, sTfR levels did not increase because cellular iron demand did not increase, and serum ferritin levels did not decrease. The increase in hsCRP in obese patients in our study supports this interpretation; however, it was notable that hepcidin levels were similar to those in the control group. Increased hepcidin synthesis during chronic inflammation decreases serum iron levels by inhibiting iron absorption from the intestinal endothelium and reducing its release from cells of the reticuloendothelial system (8, 9). Our results do not support the role of hepcidin in low serum iron levels in obese children.

In a study with 1866 participants aged 7–18 years, the relationship between iron metabolism and dyslipidemia in children was investigated, and it was found that the prevalence of iron deficiency and dyslipidemia increased according to BMI categories—8.9% and 58.3%, respectively, in cases with obesity. Those with obesity had low serum iron and high ferritin values, and children and adolescents with dyslipidemia had lower concentrations of both Tf and sTfR compared to those without dyslipidemia. In the same study, the authors concluded that low sTfR and Tf levels were associated with an increased risk of dyslipidemia, while serum iron and ferritin levels were not significantly associated with dyslipidemia (10). In our study, sTfR levels were significantly lower in the overweight dyslipidemic group compared to the non-dyslipidemic overweight group, and

no differences were found between sTfR, Tf, ferritin, serum iron, iron/ferritin, and iron/hepcidin values in the obese dyslipidemic group. Similar to the study by Wang et al. (10), who drew attention to the inverse relationship between sTfR levels and dyslipidemia risk, our finding that sTfR levels were not significantly lower in the obese group does not support this hypothesis.

There is no established algorithm in the literature to evaluate iron and lipid balance together. In our study on this topic, which has recently gained attention, a negative correlation was found between serum iron and HDL cholesterol and a positive correlation between hepcidin and LDL cholesterol and TC in obese patients. No significant correlations were observed between HDL-C, LDL-C, TC, and TG levels and Tf, TIBC, sTfR, ferritin, iron/ferritin, or iron/hepcidin values. Although the positive correlation observed between hepcidin and LDL cholesterol and TC in our study supports the potential role of hepcidin in the atherosclerotic process, no significant correlation was observed in linear regression analysis.

In our study investigating the effects of iron metabolism markers on the risk of dyslipidemia, findings from correlation analyses between groups with dyslipidemia and different BMIs did not support a significant relationship between dyslipidemia and iron metabolism. Studies examining the relationship between iron and lipid metabolism in overweight and obese children remain limited.

Studies with a larger number of participants are needed to elucidate the results we have obtained on this subject and the related mechanisms. Decreased gut microbial diversity has been associated with inflammation and body fat accumulation. In other words, the microbiota in obese individuals differs from normal characteristics. Since iron absorption occurs in the gut, changes in gut microbiota can adversely affect iron metabolism. Further research is needed in this area (11).

CONCLUSION

As a result, it can be concluded that serum iron levels in obese children are lower than in the control group. This is not due to iron deficiency but to chronic inflammation, and chronic inflammation in childhood obesity does not increase serum hepcidin levels and thus does not adversely affect lipid metabolism. Childhood-onset obesity is a chronic inflammatory disease that continues with complications into adult life. Iron parameters should be evaluated in patients with obesity in order to detect iron deficiency early and initiate treatment promptly. The relationship between iron metabolism, dyslipidemia risk, and related biomarkers should continue to be investigated.

Ethics Committee Approval: The Sakarya University Ethics Committee granted approval for this study (date: 30.12.2020, number: E.16214662-050.01.04-1732306).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This research was supported by Sakarya University Scientific Research Projects Coordination under project number 2019-6-26-12.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – PDÇ, DKÜ; Design – PDÇ, DKÜ; Supervision – PDÇ, DKÜ; Resources – PDÇ, DKÜ; Materials – PDÇ, DKÜ; Data Collection and/or Processing – PDÇ, DKÜ; Analysis and/or Interpretation – PDÇ, DKÜ; Literature Search – PDÇ, DKÜ; Writing – PDÇ, DKÜ; Critical Reviews – PDÇ, DKÜ.

Peer-review: Externally peer-reviewed.

Etik Kurul Onayı: Sakarya Üniversitesi Etik Kurulu'ndan bu çalışma için onay alınmıştır (tarih: 30.12.2020, sayı: E.16214662-050.01.04-1732306).

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Bu araştırma Sakarya Üniversitesi Bilimsel Araştırma Projeleri Koordinatörlüğü tarafından 2019-6-26-12 numaralı proje ile desteklenmiştir.

Yazma Yardımı için Yapay Zeka Kullanımı: Beyan edilmedi.

Yazarlık Katkıları: Fikir – PDÇ, DKÜ; Tasarım – PDÇ, DKÜ; Denetlemeler – PDÇ, DKÜ; Kaynaklar – PDÇ, DKÜ; Malzemeler – PDÇ, DKÜ; Veri Toplama ve/veya İşleme – PDÇ, DKÜ; Analiz ve/veya Yorumlama – PDÇ, DKÜ; Literatür Araştırması – PDÇ, DKÜ; Yazım – PDÇ, DKÜ; Eleştirel İncelemeler – PDÇ, DKÜ.

Hakemli inceleme: Harici olarak hakemli.

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