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Is level of Hepcidin among children diagnosed with iron deficiency anemia increased as suspected?

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Abstract

Introduction: The lower hepcidin levels observed among children with iron deficiency anemia may reflect a physiological compensatory mechanism in response to depleted iron stores and increased demands for erythropoiesis. Reduced hepcidin activity facilitates ferroportin-mediated intestinal iron uptake and the release of stored iron into the circulation, thereby enhancing iron availability for hemoglobin production. Nevertheless, the association between hepcidin and conventional indicators of iron status can be multifactorial, as hepcidin synthesis is additionally influenced by inflammatory processes, tissue hypoxia, and the degree of erythropoietic activity. In this study assessment of hepcidin among confirmed diagnosis of iron deficiency anemia (IDA) children in order to evaluate the concept of hepcidin related to diminished iron body content.

Methodology

55 IDA were recruited, serum iron, ferritin and total iron binding capacity were assessed beside complete blood count parameters. Comparison conducted with reference ranges of measured parameters. Hepcidin was assessed by statistical package of social science (SPSS0 version 20. Children involved with their guardians' approval.

Result

Among children with IDA have measured parameters. Comparison hematological parameters, iron profile and hepcidin with reference mid points showed that there were significant differences in all parameters (p value for each <0.05) (Hb, red blood cell indices, serum iron, ferritin and hepcidin were lower than normal range, TIBC was increased than normal range) except WBC, for which p value was >0.05. Considering genders, comparing measured parameters between males and females no significant differences obtained as for each parameter p value was >0.05.

Conclusion

There was decreased level of hepcidin among children with IDA than reference range.

key words: Hepcidin, iron deficiency anemia, total iron binding capacity

Introduction

Anemia is among the most prevalent health disorders globally, with iron-deficiency ane-

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mia recognized as its most common form. It occurs when the body's total iron stores are insufficient to meet the high iron requirements of the bone marrow for effective red blood cell production, ultimately reducing the capacity to maintain adequate oxygen delivery to tissues (1).

Iron availability is primarily regulated by the liver-derived peptide hormone hepcidin. Increased body iron stimulates hepcidin production and its release into the circulation, where it acts on ferroportin, a transmembrane iron-export protein abundantly expressed on intestinal enterocytes, macrophages, and hepatocytes. Hepcidin decreases the amount of iron entering the circulation from duodenal absorptive cells and iron-recycling macrophages by inhibiting ferroportin-mediated iron export and promoting ferroportin degradation. Through its regulation of circulating iron levels and systemic iron homeostasis, the hepcidin–ferroportin axis plays an important role in erythropoiesis and may therefore influence the development of anemia. Hepcidin synthesis is regulated through interaction between liver sinusoidal endothelial cells (LSECs), which produce bone morphogenetic proteins (BMPs), and hepatocytes, which synthesize and secrete hepcidin. Among these signaling molecules, BMP6 and BMP2 are major stimulators of hepcidin expression, with BMP6 production being particularly responsive to body iron levels (2).

Hepcidin was first isolated from urine and plasma on the basis of its structural similarities to antimicrobial peptides and named for its origin in the liver and its antimicrobial properties in vitro (3). It is a 25-amino-acid peptide hormone synthesized primarily by the liver and is considered an important mediator of anemia associated with inflammation. It serves as the major regulator of systemic iron balance. When the body requires additional iron for erythropoiesis, hepcidin synthesis is suppressed, increasing iron availability for red blood cell production. Conversely, inflammatory conditions, particularly those involving interleukin-6 (IL-6), stimulate hepcidin production and release. Hepcidin regulates iron transport by binding to ferroportin, an iron-export protein expressed on intestinal enterocytes, macrophages, and hepatocytes. This interaction promotes ferroportin internalization and lysosomal degradation, resulting in retention of iron within these cells and consequently causing a rapid reduction in circulating plasma iron levels (4).

Iron availability is primarily regulated by the liver-derived peptide hormone hepcidin. Increased body iron stimulates hepcidin production and its release into the circulation, where it acts on ferroportin, a transmembrane iron-export protein abundantly expressed on intes-

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Iron-deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide. It can develop due to insufficient dietary iron intake, reduced intestinal absorption, or excessive iron loss resulting from conditions such as menstrual or gastrointestinal bleeding. Treatment generally involves oral or intravenous iron supplementation. Although oral iron is commonly used as the first-line therapy, some patients experience gastrointestinal side effects, poor tolerance, or an inadequate response within the expected treatment period. Furthermore, inflammation and other underlying conditions can interfere with intestinal iron absorption and impair the release of stored iron for use by hematopoietic cells, thereby limiting the effectiveness of iron therapy (5).

Hepcidin is synthesized at a relatively high rate under normal physiological conditions and is rapidly eliminated from the bloodstream through renal clearance, resulting in a very short half-life of only a few minutes. Consequently, changes in the rate of hepcidin production can quickly alter its circulating levels and, in turn, influence the amount of iron released into the plasma. Current evidence indicates that hepcidin regulation occurs primarily at the transcriptional level. The main factors controlling hepcidin gene expression include circulating plasma iron concentration, hepatic iron stores, inflammation, and the rate of erythropoiesis (3). Dysregulation of hepcidin production plays an important role in the development of several disorders of iron metabolism. Insufficient hepcidin production can lead to excessive iron accumulation, as observed in conditions such as hereditary hemochromatosis and □-thalassemia. In contrast, excessive hepcidin production restricts iron availability and contributes to iron-restricted anemia associated with chronic kidney disease, autoimmune inflammatory conditions, certain cancers, and inherited iron-refractory iron-deficiency anemia. Therefore, maintaining appropriate hepcidin regulation is es-

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sential for normal iron homeostasis and the prevention of iron-related diseases. A better understanding of the molecular pathways controlling hepcidin expression is consequently important for elucidating the underlying mechanisms of iron disorders (6).

Material and method

This study was targeting patients with iron deficiency anemia, they were 55 patients, males were 27 and females were 28. They diagnosed with IDA by measuring serum iron, ferritin and total iron binding capacity from plasma separated from whole blood samples collected in heparin added blood containers, iron profile conducted via suitable reagents and device semi- automated chemical analyzer (BTS350) plus., complete blood count (CBC) parameters were measured by Mindray BC3000 and hepcidin level measured by enzyme linked immune sorbent assay (ELISA). Statistical analysis by statistical package of social science (SPSS) version 20.

Result

This cross sectional study was conducted among patients diagnosed with iron deficiency anemia in order to evaluate hepcidin state among them. They were 50.9% females and 49.1% males as in figure 1.

Age of participants ranged from 1 to 15 years with mean+SD 6.9+3.8 years. As in table 1, in which parameters assessed were shown. Serum iron, ferritin, total iron binding capacity and hepcidin.

Comparison hematological parameters with reference mid points showed that there were significant differences in all parameters (p value for each <0.05) (Hb, red blood cell indices, serum iron, ferritin and hepcidin were lower than normal range, TIBC was increased than normal range) except WBC, for which p value was >0.05 as in table 2.

Considering genders, comparing measured parameters between males and females no significant differences obtained as for each parameter p value was >0.05 as in table 3

Pearson's correlation of age with measured parameters showed positive correlations with Hb, PCV, MCH, Ferritin, TIBC, neutrophil % and negative with the rest of parameters but no significant differences obtained as in table 4

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Figure 1: Distribution of Participants by Gender (N = 55)

Table 1: Descriptive Statistics of Hematological and Iron Profile Parameters Among Participants (N = 55)

Variable	Min–Max	Mean ± SD
Age	15–1	3.8 ± 6.9
HB	13.9–4.2	2.1 ± 9.4
PCV	46–2	6.9 ± 29.7
MCH	76.0–14.0	8.2 ± 22.9
MCHC	33–24	2.4 ± 29.9
MCV	373–31	42.0 ± 76.3
RBC	6.9–2.2	0.7 ± 4.2
WBC	11.0–2.4	2.2 ± 7.3
Neutrophils	74–22	11.3 ± 39.7
Lymphocytes	72–17	12.0 ± 49.8
Mixed cells	22–1	4.0 ± 9.0
Platelets	806–54	133.2 ± 324.0
Serum Iron	200–3	39.9 ± 82.0
Ferritin	51.6–0.8	12.8 ± 13.2
TIBC	908–81	155.3 ± 400.3
Hepcidin	71.7–1.1	16.0 ± 23.0

Table 2: Comparison of Hematological and Iron Indices Against Reference Midpoint Values

Parameter	Mean ± SD	Reference	p-value
RBC	0.7 ± 4.2	4.4	*0.023
HB	2.1 ± 9.4	15.7	*0.001>
PCV	6.9 ± 29.7	44.0	*0.001>
MCV	42.0 ± 76.3	90.5	*0.015
MCH	8.2 ± 22.9	29.5	*0.001>
MCHC	2.4 ± 29.9	33.0	*0.001>
WBC	2.2 ± 7.3	7.0	0.375
Neutrophils	11.3 ± 39.7	60.0	*0.001>
Lymphocytes	12.0 ± 49.8	35.0	*0.001>
Mixed cells	4.0 ± 9.0	6.0	*0.001>
Platelets	133.2 ± 324.0	300.0	0.186
Serum Iron	39.9 ± 82.0	112.5	*0.001>
Ferritin	12.8 ± 13.2	182.5	*0.001>
TIBC	155.3 ± 400.3	337.5	*0.004
Hepcidin	16.0 ± 23.0	70.0	*0.001>

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Table 3: Comparison of Hematological and Iron Profile Parameters by Gender (N = 55)

Variable	(Male) n = 27	(Female (n = 28	p-value
HB	2.1 ± 9.6	2.1 ± 9.2	0.424
PCV	5.6 ± 31.0	7.9 ± 28.4	0.171
MCH	11.1 ± 24.3	3.2 ± 21.5	0.208
MCHC	2.7 ± 29.6	2.0 ± 30.2	0.333
MCV	12.2 ± 71.9	57.8 ± 80.5	0.454
RBC	0.8 ± 4.2	0.6 ± 4.2	0.831
WBC	2.5 ± 7.2	1.9 ± 7.3	0.875
Neutrophils	11.9 ± 39.4	11.0 ± 39.9	0.885
Lymphocytes	12.2 ± 48.9	11.9 ± 50.7	0.576
Mixed cells	4.3 ± 9.9	3.5 ± 8.1	0.098
Platelets	120.8 ± 308.3	144.7 ± 339.2	0.395
Serum Iron	38.3 ± 83.3	42.0 ± 80.8	0.821
Ferritin	13.8 ± 15.4	11.6 ± 11.1	0.221
TIBC	134.4 ± 391.7	175.2 ± 408.5	0.691
Hepcidin	12.9 ± 20.8	18.4 ± 25.2	0.314

Table 4: Correlation of Age with Hematological and Iron Profile Parameters (N = 55)

Variable	Pearson Correlation (r)	p-value
HB	0.027	0.843
PCV	0.039	0.775
MCH	0.213	0.118
MCHC	-0.207	0.129
MCV	-0.193	0.158
RBC	-0.231	0.090
WBC	-0.245	0.071
Neutrophils	0.256	0.059
Lymphocytes	-0.206	0.131
Mixed cells	-0.119	0.385
Platelets	-0.274	***0.043**
Serum Iron	-0.103	0.456
Ferritin	0.039	0.777
TIBC	0.007	0.958
Hepcidin	-0.040	0.774

Discussion:

The present cross-sectional study evaluated hematological indices, iron profile parameters, and serum hepcidin levels among 55 children aged 1–15 years diagnosed with iron

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deficiency anemia (IDA). The participants were almost equally distributed by sex, with females comprising 50.9% and males 49.1%. The mean age of the participants was 6.9 ± 3.8 years. The relatively balanced distribution between males and females provides an opportunity to examine whether sex-related differences influence hematological and iron-status parameters in children with IDA.

The hematological findings demonstrated a clear pattern consistent with iron deficiency anemia. The mean hemoglobin concentration was 9.4 ± 2.1 g/dL, while the mean PCV was 29.7 ± 6.9%. In addition, the mean MCH (22.9 ± 8.2 pg), MCHC (29.9 ± 2.4 g/dL), and MCV (76.3 ± 42.0 fL) were generally reduced compared with the reference midpoint values. These findings indicate impaired hemoglobin synthesis and are compatible with the typical microcytic and hypochromic pattern associated with iron deficiency. Similar findings have been reported in previous pediatric studies. For example, a study of children with IDA found significantly lower hemoglobin, MCV, MCH, and MCHC compared with healthy controls. Another study involving 59 children with iron deficiency or IDA also demonstrated significant differences in hemoglobin and other iron-related hematological indices between IDA, iron-deficient, and control groups.

The significantly decreased serum iron concentration observed in the present study (82.0 ± 39.9) provides further evidence supporting the presence of iron deficiency. Similarly, serum ferritin levels were substantially reduced, with a mean value of 13.2 ± 12.8, suggesting considerable depletion of body iron stores. In contrast, TIBC was significantly elevated (400.3 ± 155.3). This pattern of low serum iron and ferritin accompanied by increased TIBC is typical of iron deficiency and reflects the body's physiological adaptation to insufficient iron availability. The elevation in TIBC is primarily attributable to increased hepatic synthesis of transferrin, which enhances the capacity to bind and transport the limited iron available in circulation. These findings are consistent with previous study (**Saeed MK et al 2026**) (7) conducted among children with iron deficiency anemia (IDA), which have similarly documented decreased serum iron and ferritin concentrations alongside elevated TIBC. For example, a recent study involving children aged 2–10 years found significantly lower serum iron levels and higher TIBC among children with IDA compared with healthy controls. Furthermore, earlier pediatric studies have reported an inverse relationship between hepcidin and TIBC, while hepcidin showed positive associations with serum iron and ferritin, supporting the interconnected roles of hepcidin and conventional iron-status indicators in the regulation of iron metabolism.

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An important finding of the present study was the significantly reduced serum hepcidin concentration compared with the stated reference midpoint, with a mean value of 23.0 ± 16.0. Hepcidin is the major hormonal regulator of systemic iron homeostasis. Under conditions of adequate or increased iron stores, hepcidin production increases and limits intestinal iron absorption and iron release from macrophages by inducing internalization and degradation of ferroportin. In contrast, iron deficiency and increased erythropoietic demand suppress hepcidin production, thereby facilitating intestinal iron absorption and mobilization of stored iron. Therefore, the relatively low hepcidin level observed in these children is physiologically consistent with iron deficiency and represents an appropriate compensatory response to depleted iron stores.

This finding is in agreement with several pediatric studies. A study by (**Hyoung Soo Choi et al 2012**) (8) involving 59 children aged 5 months to 17 years reported substantially lower serum hepcidin in children with IDA than in healthy controls, with mean concentrations of 2.01 ± 2.30 ng/mL and 16.71 ± 14.74 ng/mL, respectively. Hepcidin was positively correlated with ferritin, serum iron, transferrin saturation, and hemoglobin, while it was negatively correlated with TIBC. Similarly, (**Dewan P et al 2019**) (9), reported significantly lower serum hepcidin concentrations among children younger than five years with IDA compared with healthy children. More recently, a pediatric study of 90 children found that hepcidin-25 was significantly lower in both early iron deficiency and IDA than in controls, and hepcidin showed positive relationships with serum iron and ferritin and an inverse relationship with TIBC.

The findings are also consistent with a study of 173 children and adolescents with IDA by (**ulafi J et al 2018**) (10), in which reported substantially lower hepcidin concentrations among iron-deficient children compared with controls. That study also demonstrated positive associations between hepcidin and serum iron, ferritin, MCV, and transferrin saturation, while inverse relationships were observed with transferrin and reticulocytes. Collectively, these findings support the concept that hepcidin responds dynamically to body iron stores and erythropoietic requirements.

The lower hepcidin concentration in IDA can also be explained by increased erythropoietic drive. Iron deficiency reduces oxygen delivery and stimulates erythropoietic activity, which promotes production of erythroferrone by erythroid precursors. Erythroferrone suppresses hepatic hepcidin synthesis, thereby increasing iron availability for erythropoiesis. Evidence

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from pediatric IDA research supports this mechanism. In one study, erythroferrone concentrations were significantly elevated in children with IDA and were negatively correlated with hemoglobin, serum iron, transferrin saturation, and ferritin, while being positively correlated with TIBC. Thus, the reduced hepcidin observed in the present study may reflect the combined effects of depleted iron stores and increased erythropoietic demand.

Despite the low hepcidin level, the mean value in the present study was considerably higher than values reported in some pediatric studies. This difference should not necessarily be interpreted as evidence of increased hepcidin production. Hepcidin measurements are strongly influenced by the analytical method, assay calibration, sample type, and whether the assay measures mature hepcidin-25 or related hepcidin forms. Previous research has highlighted substantial differences in absolute hepcidin values between analytical assays, even when measurements within individual laboratories correlate well. Therefore, direct comparison of absolute hepcidin concentrations between studies should be undertaken cautiously unless the same assay and analytical platform were used.

With respect to white blood cells, the mean WBC count was $7.3 \pm 2.2 \times 10^{\square}$/L and did not differ significantly from the reference midpoint. This suggests that IDA in the studied children was not associated with a major alteration in total leukocyte count. In contrast, significant differences were observed in neutrophil, lymphocyte, and mixed-cell percentages. The relatively higher lymphocyte percentage and lower neutrophil percentage may partly reflect the young age distribution of the participants, because differential leukocyte counts vary considerably during childhood. Importantly, these findings should not be interpreted as evidence that iron deficiency itself directly caused the differential count changes without considering other factors such as age, nutritional status, recent infection, or inflammatory conditions.

The platelet count was not significantly different from the reference midpoint, although the mean value was relatively high ($324.0 \pm 133.2 \times 10^{\square}$/L). Reactive thrombocytosis is recognized in some children with iron deficiency, although it is not present in all patients. The absence of a significant difference in the current study may indicate that platelet responses were variable among participants. The relatively large standard deviation also suggests considerable inter-individual variation.

Comparison of hematological and iron-related parameters according to sex showed no significant differences between males and females. Hemoglobin, PCV, MCV, MCH, serum

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iron, ferritin, TIBC, and hepcidin were statistically comparable between the two groups. These findings suggest that, within this pediatric population, iron deficiency and its associated hematological and hepcidin responses were not substantially influenced by sex. This is plausible because the participants were children and therefore had not yet developed the physiological differences in iron requirements that become more prominent after puberty, particularly in females because of menstrual blood loss. Previous pediatric study (**Jaeggi T et al 2013**) (11) have similarly included both male and female children without identifying a major sex-related difference in the overall iron-deficiency pattern. For example, studies evaluating hepcidin in children have included mixed-sex populations and demonstrated the principal differences according to iron status rather than sex.

The correlation analysis demonstrated that age was not significantly associated with most hematological or iron-profile parameters. Although age showed weak positive correlations with hemoglobin ($r = 0.027$), PCV ($r = 0.039$), MCH ($r = 0.213$), ferritin ($r = 0.039$), and TIBC ($r = 0.007$), none reached statistical significance. Negative correlations were observed with MCHC, MCV, RBC count, WBC count, lymphocytes, mixed cells, serum iron, and hepcidin, but these associations were also statistically no significant. These findings suggest that within the relatively broad age range of 1–15 years, age alone did not substantially explain variation in iron status or hepcidin concentrations, a partial agreement obtained by outcomes of a study Compared with healthy controls, the iron-deficient group had significantly lower hemoglobin ($p < 0.001$), MCV ($p = 0.001$), MCH ($p < 0.001$), MCHC ($p < 0.001$), iron ($p < 0.001$), ferritin ($p < 0.001$) and hepcidin ($p = 0.001$). Ferritin and hepcidin levels increased while erythroferrone levels remained unchanged after iron deficiency treatment. There was no correlation between hepcidin and ferritin levels in treatment group. The study found a strong and positive correlation between ferritin and hepcidin levels in iron-deficient children, but not between ERFE levels, suggesting that hepcidin is largely regulated by iron deposition levels (**Dulkadir R et al 2024**) (12).

The absence of a significant association between age and hepcidin is consistent with previous research. A study involving children and adolescents with IDA reported that age did not significantly influence serum hepcidin concentration and concluded that hepcidin may provide a useful indicator of body iron status across different pediatric age groups. Similarly, the present study found virtually no correlation between age and hepcidin ($r = \square 0.040$, $p = 0.774$). This suggests that the reduction in hepcidin in these children was more likely related to their iron-deficient state than to age-related physiological variation.

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A significant negative correlation was identified between age and platelet count ($r = -0.274$, $p = 0.043$). Although this association was statistically significant, its magnitude was weak. Therefore, age explained only a small proportion of the variation in platelet count. This finding may reflect age-related physiological changes in hematological parameters rather than a direct effect of iron deficiency. Because the study was cross-sectional, a causal relationship cannot be established.

None of the measured iron parameters showed a significant correlation with hepcidin in the present study. Hepcidin demonstrated a weak negative correlation with serum iron ($r = 0.103$, $p = 0.456$), a very weak negative correlation with age ($r = -0.040$, $p = 0.774$), and no meaningful association with ferritin ($r = 0.039$, $p = 0.777$) or TIBC ($r = 0.007$, $p = 0.958$). These findings differ from several previous studies that reported significant positive correlations between hepcidin and ferritin, serum iron, transferrin saturation, and hemoglobin, as well as negative correlations with TIBC (**ulafi J et al 2018**) (10).

Several explanations may account for this discrepancy. First, the present study included only children already diagnosed with IDA, resulting in a relatively homogeneous population with generally depleted iron stores. Restriction of the study population to one disease state can reduce the range of iron parameters and consequently weaken detectable correlations. In contrast, studies that included healthy controls, children with iron deficiency without anemia, and children with IDA had a wider biological range of iron status and were therefore better able to identify correlations between hepcidin and iron indices (**ulafi J et al 2018**) (10).

Second, hepcidin is regulated by several competing physiological pathways. Although iron deficiency suppresses hepcidin, inflammation increases it through the IL-6 pathway, while erythropoietic activity suppresses it. Consequently, variations in infection, inflammation, nutritional status, erythropoietic activity, and other clinical factors may influence hepcidin independently of serum iron or ferritin. A pediatric study comparing anemia of chronic disease with IDA demonstrated markedly higher hepcidin concentrations in inflammatory anemia than in IDA, illustrating the strong influence of inflammatory signaling on hepcidin regulation (**Mahajan G et al 2017**) (13).

Third, ferritin is an acute-phase protein and may be influenced by inflammation, infection, or other conditions. Therefore, ferritin does not always represent iron stores independently of inflammatory status. This is particularly relevant in pediatric populations, where subclin-

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ical infections may occur frequently. Previous research has emphasized the limitations of ferritin in the presence of inflammation and has suggested that hepcidin may provide complementary information regarding iron metabolism. The absence of CRP or IL-6 measurements in the present study limits the ability to determine whether inflammatory signaling contributed to the observed variability in hepcidin (**WHO 2020**) (14).

The findings of this study indicate that the children demonstrated a biochemical and hematological profile consistent with iron deficiency anemia (IDA), characterized by decreased hemoglobin and red-cell indices, reduced serum ferritin and iron concentrations, elevated total iron-binding capacity (TIBC), and lower hepcidin levels compared with the reference value. The absence of statistically significant differences between males and females suggests that these hematological and iron-related abnormalities were generally comparable across both sexes. Similarly, age was not significantly associated with hepcidin concentrations or with most of the assessed iron parameters (15).

The reduced hepcidin levels observed in these children are biologically plausible and may reflect a compensatory physiological response to iron depletion and the increased iron requirements associated with active erythropoiesis. Nevertheless, the absence of significant associations between hepcidin and conventional iron-status parameters in the present study contrasts with findings reported in several previous pediatric studies. This discrepancy may be attributable to the relatively small sample size, the inclusion of children with established IDA only, differences in hepcidin measurement techniques, and the lack of additional markers reflecting inflammation and erythropoietic activity (8).

Conclusion

The findings of the present study highlight the potential importance of hepcidin in maintaining iron homeostasis among children with iron deficiency anemia (IDA). Although hepcidin levels were reduced in the studied children, the absence of significant correlations with conventional iron-status parameters indicates that its regulation is multifaceted and may not be determined solely by body iron stores. Further studies examining hepcidin in conjunction with inflammatory and erythropoietic markers may provide deeper insight into the mechanisms governing iron metabolism in children with IDA.

Recommendation

Future studies should recruit larger sample populations and incorporate both healthy con-

trols and children with iron deficiency without anemia to provide a broader assessment of hepcidin regulation. The inclusion of inflammatory and erythropoietic biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), transferrin saturation, soluble transferrin receptor, and erythroferrone, would help clarify the complex mechanisms influencing hepcidin levels during pediatric iron deficiency. In addition, greater standardization of hepcidin measurement methods is needed to improve comparability among studies and to facilitate the development of reliable pediatric reference intervals and clinically meaningful diagnostic thresholds.

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