Hepcidin profile

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Hepcidin profile of anemic adolescent schoolgirls in Indonesia at the end of 12 weeks of iron supplementation

Min Kyaw Htet, Drupadi Dillon, Azma Rosida, Ina Timan, Umi Fahmida, and David I. Thurnham

Abstract

Background. *Iron deficiency is still the major nutritional problem in the developing world, and iron supplementation remains one of the most effective intervention strategies. Hepcidin, a newly discovered iron regulatory hormone, is an acute phase protein, and its role in iron supplementation has not been well explored.*

Objective. *To investigate the hepcidin profiles of anemic adolescent girls who had received weekly iron supplementation.*

Methods. *A cross-sectional study was conducted at the end of iron supplementation among adolescent schoolgirls (n = 83) in Pramuka Island, Indonesia. All the girls were anemic at the beginning and received 60 mg of elemental iron twice weekly for 12 weeks. Hemoglobin, hepcidin, serum ferritin, and red cell parameters were measured, together with inflammation markers.*

Results. *At the end of the 12-week supplementation, 65.1% (n=64) of the girls were no longer anemic, but 43.4% (n = 36) were still iron deficient. The rate of subclinical inflammation, measured by C-reactive protein (CRP) and* α*-1-acid glycoprotein (AGP), was 38.6% (n = 32). Hepcidin was not correlated with either ferritin or red cell parameters. There was no association between hepcidin and the inflammatory markers CRP and AGP. The mean hepcidin concentration was 42.9 ± 17.9 ng/mL and was not significantly different between anemic and nonanemic girls (44.2 ± 14.9 and 42.3 ± 19.2 ng/mL, respectively; p = .708). However, hepcidin concentration was slightly higher in the iron replete-group than in the iron-deficient group (45.2 ± 20.0 and 39.3 ± 13.5 ng/mL, respectively), a suggestive trend that did not reach statistical significance (p = .218).*

Conclusions. *Hepcidin concentrations tended to be higher among the subset of girls who responded poorly to iron supplementation as a consequence of increased subclinical inflammation. A longitudinal study should be conducted to explore the role of hepcidin in iron supplementation.*

Key words: Adolescent schoolgirls, hepcidin, Indonesia, inflammation, iron deficiency

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Introduction

Whether the nutritional status of an individual is synergistically or antagonistically affected by infection has been an interesting issue over the past few decades. The monograph on "Interactions of nutrition and infection" by Scrimshaw and colleagues provided strong evidence for the importance of infection in leading to clinical malnutrition and the impact of malnutrition on morbidity and mortality due to infections [1]. Every infection and trauma is accompanied by an acute phase response. The main purpose of this response is to assist in removing harmful molecules and pathogens and minimizing damage to tissues [2]. An acute phase protein can be defined as one whose plasma concentration increases (positive acute phase

protein) or decreases (negative acute phase protein) by at least 25% during inflammatory disorders [3]. The acute phase reaction can be usually monitored by two inflammatory markers, C-reactive protein (CRP) and α-1-acid glycoprotein (AGP). These two acute phase proteins can also identify the three stages of subclinical infection and inflammation: incubation and early and late convalescence phase [4]. The acute phase reaction or subclinical inflammation can exist in an apparently healthy population, and unless taken into account, it can interfere with the assessment of micronutrient status, especially iron and vitamin A status indicators [5–7].

Anemia is one of the major nutritional problems in developing countries, and iron deficiency is regarded as the major contributor to the high prevalence of anemia [8]. For many years, iron supplementation has been one of the main strategies to tackle anemia [9, 10]; yet the complex nature of iron metabolism has not been well taken into account in the context of iron supplementation. The landmark study of routine iron supplementation among preschool children in the malaria-endemic area in Zanzibar demonstrated the complex mechanism of iron metabolism. In that study, the children who received iron supplements had an increased risk of severe adverse events (death or severe morbidity leading to hospital admission) compared with those who received placebo, a result that highlighted the potential adverse consequences of universal iron supplementation [11]. The newly discovered iron regulatory hormone, hepcidin, provides an explanation for anemia in the presence of chronic inflammation and infections [12]. Hepcidin, a negative iron regulatory hormone, is mainly released from the liver by stimulation of the proinflammatory cytokine interleukin-6 during infection and inflammation and acts through the inhibition of both intestinal iron absorption and the release of storage iron [13]. Hepcidin is one of the acute phase proteins and is considered the master regulator of host iron absorption. It is a potential indicator to assess the success of an intervention, as it can reflect the incorporation of iron into erythrocytes during iron supplementation [14].

The role of hepcidin in iron metabolism has been studied mainly *in vitro*, and data from human studies are scanty, especially for healthy subjects. The present study was undertaken among healthy adolescent schoolgirls to investigate the profile of hepcidin in relation to iron status at the end of 12 weeks of iron supplementation. We hypothesized that hepcidin concentration would be higher among those who were still anemic and did not respond well to iron supplementation. Furthermore, we compared the hepcidin concentration in responders and nonresponders to iron supplementation. We also investigated the relationship between subclinical inflammation and hepcidin.

Materials and methods

Participants

The study was conducted in Pramuka Island in the Bay of Jakarta in March 2009 among adolescent girls attending one junior high school and one senior high school. The area is located about 45 km from the capital city of Jakarta. The study was a cross-sectional study conducted at the end of the 12 weeks of iron supplementation. All the girls (n = 83) were anemic (hemoglobin < 120 g/L) at baseline and received iron tablets (ferrous sulfate providing 60 mg of elemental iron) twice weekly for 12 weeks.

Ethical approval

The parents and school authorities were informed about the objectives of the study, and informed consent was obtained from all subjects. Ethical approval of the study was granted by the Faculty of Medicine, University of Indonesia.

Laboratory assessment

Hemoglobin level was measured by the HemoCue method. Phlebotomy was performed by an experienced nurse; 3 mL of nonfasting venous blood was taken from each subject in the morning school session. The blood samples were collected into nonheparinized vacuettes as well as into ethylenediaminetetraacetate (EDTA) tubes and transported in ice-cooled containers to the laboratories. The red cell parameters were measured by Sysmex XT-2000i, and serum hepcidin concentrations were determined with a commercial ELISA kit (DRG Instruments). CRP was measured by the immunometric sandwich method using a NycoCard CRP-single test (CRP-N, Axis-Shield), and serum ferritin was measured by the Roche Tina-quant Ferritin immunoturbidimetric assay on the Hitachi 912 clinical analyzer (Roche Diagnostics). The chronic inflammation marker AGP was measured by an in-house sandwich enzyme-linked immunosorbent method [15]. Anemia was defined as hemoglobin concentration < 12.0 mg/dL, and iron deficiency as serum ferritin < 15 µg/L. The data for analysis of hepcidin were available for only 59 randomly selected subjects.

Anthropometric assessment

Body weight was measured with a flat electronic weighing scale (SECA 872) to the nearest 0.1 kg, and height was measured with a wooden measuring board (Shorrboard, Shorr Productions) to the nearest 0.1 cm. Nutritional status was assessed by z-scores, and World Health Organization (WHO) Anthro-Plus software was used for the analysis. Stunting was defined as

a height-for-age z-score < –2 SD and thinness was defined as a body mass index (BMI)-for-age z-score < –2 SD [16]. BMI is the weight in kilograms divided by the square of the height in meters.

Statistical analysis

Statistical analyses were performed with the statistical software package SPSS, version 15.0 for Windows. Normality of distribution of the variables was checked with the Komogorov–Smirnov test, and the data were transformed if they were not normally distributed. Serum ferritin and CRP were log transformed to better approximate a normal distribution. Data are presented as means ± SD or geometric means (95% CI) for continuous variables and as proportions for categorical data. Pearson's correlation test was used to investigate the relationship between hepcidin and other iron status indicators and markers of inflammation. Independent-sample *t*-tests were used to compare the mean difference between anemic and nonanemic and between iron-deficient and non-iron-deficient subjects at endline. The value of serum ferritin was corrected using the meta-analysis correction factors [6]. Correction factors were also calculated using data from the present study, but the small numbers of subjects in some groups made the results unreliable.

TABLE 1. Nutritional status and nutrition-related indicators of the adolescent schoolgirls at the end of 12 weeks of iron supplementation ($n = 83$)

Variable	Value[a]	No. (%)
Weight (kg)	46.6 ± 7.2	
Height (cm)	153.0 ± 2.8	
BMI	19.9 ± 2.8	
Underweight (BMI < 18.5)		26 (31.3)
HAZ	–1.2 ± 0.8	
BAZ	–0.3 ± 1.1	
Stunting (HAZ < –2 SD)		12 (14.5)
Thinness (BAZ < –2 SD)		5 (6.0)
Hemoglobin at baseline (mg/dL)	10.7 ± 1.1	
Hemoglobin at endline (mg/dL)	12.1 ± 1.6	
Anemia at endline		29 (34.9)
Serum ferritin (original) (μg/L)	20.3 (23.6, 38.7)	
Iron deficiency[b]		33 (39.8)
Serum ferritin, corrected (μg/L)[c]	17.8 (21.0, 33.5)	
Iron deficiency after correction[c]		36 (43.4)
CRP (mg/L)	5.0 (4.9, 5.7)	
CRP > 5 mg/L		4 (4.8)
AGP (g/L)	0.9 ± 1.3	
AGP > 1 g/L		29 (34.9)
Subclinical inflammation[d]		32 (38.6)
Hepcidin (ng/mL)	42.9 ± 17.9	

AGP, α-1-acid glycoprotein; BAZ, BMI-for-age z-score; BMI, body mass index; CRP, C-reactive protein; HAZ, height-for-age z-score
a. Mean ± SD or median (95% CI).
b. Iron deficiency was defined by serum ferritin < 15 μg/L.
c. Serum ferritin was corrected by meta-analysis correction factors obtained from Thurnham et al. [6].
d. Subclinical inflammation was defined by CRP > 5 mg/L and/or AGP > 1 g/L.

Results

The mean age of the girls was 15.6 ± 1.8 years. Anthropometric measurements showed that 14.5% ($n = 12$) of the girls were stunted and 6.0% ($n = 5$) were wasted (**table 1**). All of the girls were anemic at baseline; and the prevalence of anemia was reduced to 34.9% ($n = 29$) at endline. The mean hepcidin concentration was 42.9 ± 17.9 ng/mL. The prevalence of iron deficiency increased from 39.8% ($n = 33$) to 43.4% ($n = 36$) after ferritin was adjusted by the meta-analysis correction factor. However, the prevalence did not change when we applied the study-generated correction factor calculated from the present data, 39.8% with and without correction (data not shown).

The relations among the iron status indicators were examined and revealed that hemoglobin was significantly associated with serum ferritin ($r = 0.42$, $p < .001$). No association was observed between hepcidin and iron status indicators or inflammatory biomarkers (**table 2**).

Table 3 shows red cell parameters and inflammation status in anemic and nonanemic subjects. Red cell parameters, such as hematocrit (HCT), mean cell

TABLE 2. Relationship between hepcidin and other biomarkers among the schoolgirls at the end of 12 weeks of iron supplementation ($n = 59$)

Variable	Correlation coefficient	*p*
Hemoglobin at endline (g/dL)[a]	0.01	.94
HCT (%)[a]	–0.01	.93
MCV (fL)[a]	–0.03	.80
MCH (pg)[a]	0.00	.97
MCHC (g/dL)[a]	0.07	.61
SF adjusted by ICF (μg/L)[b]	0.17	.20
SF adjusted by MCF (μg/L)[b]	0.19	.16
CRP (mg/L)[b]	–0.11	.42
AGP (g/L)[a]	0.19	.14

AGP, α-1-acid glycoprotein; CRP, C-reactive protein; HCT, hematocrit; ICF, correction factors calculated from the present study; MCF, meta-analysis correction factor; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; SF, serum ferritin
a. Pearson's correlation coefficient.
b. Spearman's correlation coefficient.

TABLE 3. Iron status and inflammatory status in anemic and nonanemic subjects[a]

Variable	Anemia (n = 29)	No anemia (n = 54)	p^b	Total (n = 83)
HCT (%)	33.1 ± 3.1	39.0 ± 2.4	< .001	36.95 ± 3.90
MCV (fL)	73.4 ± 7.3	82.8 ± 5.0	< .001	79.49 ± 7.38
MCH (pg)	23.2 ± 3.0	27.6 ± 1.9	< .001	26.04 ± 3.11
MCHC (g/dL)	31.6 ± 1.4	33.3 ± 1.0	< .001	32.68 ± 1.40
RBC	4.5 ± 0.3	4.7 ± 0.4	.017	4.66 ± 0.40
SF (µg/L)	6.7 (4.5, 10.1)	25.9 (21.0, 32.0)	< .001	16.2 (12.7, 20.5)
CRP (mg/L)	5.0 ± 0.0	5.4 ± 2.2	.327	5.3 ± 1.8
AGP (g/L)	0.9 ± 1.3	0.9 ± 1.3	.817	0.91 ± 1.30
Hepcidin (ng/mL)[c]	44.2 ± 14.9	42.3 ± 19.2	.708	42.9 ± 17.9

AGP, α-1-acid glycoprotein; CRP, C-reactive protein; HCT, hematocrit; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell count; SF, serum ferritin
a. Geometric mean (95% CI) for SF and arithmetic mean ± SD for HCT, MCV, MCH, MCHC, RBC, CRP, AGP, and hepcidin.
b. Independent-sample t-test, significant at $p < .05$.
c. Hepcidin data were available for only 59 subjects (18 with anemia and 41 with no anemia).

volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), and red blood cell count (RBC), were significantly higher in nonanemic than in anemic subjects, but there were no differences in biomarkers of inflammation. The mean hepcidin concentration did not differ significantly between anemic and nonanemic subjects (44.2 ± 14.9 and 42.3 ± 19.2 ng/mL, respectively; p = .708).

The hemoglobin concentration at endline and the change in hemoglobin concentration from baseline to endline were significantly higher in the iron-replete than in the iron-deficient group ($p < .001$). The mean hepcidin concentration in the iron- deficient group (39.3 ± 13.5 ng/mL; n = 36) was slightly lower than that in the iron-replete group (45.2 ± 20.0 ng/mL; n = 23) (p = .218), suggesting a nonsignificant trend (**table 4**).

Discussion

Our findings showed that, at the end of the 12-week iron supplementation, 65.1% (n = 54) of the girls were no longer anemic, but 20.4% (n = 11) of those who were no longer anemic were still iron deficient. In total, 43.4% (n = 36) were still iron deficient. Iron deficiency was associated with slightly, but not significantly, lower hepcidin concentration, whereas anemia status was not related to hepcidin concentration. Hepcidin concentration was not correlated with either hemoglobin or ferritin concentration. Subclinical inflammation was also present among the girls (38.6%, n = 32) but was not associated with hepcidin concentration.

Anemia is common in Indonesia [17–19], but data on iron deficiency are scanty, especially for adolescents. According to published data, the prevalence of iron deficiency among adolescents is estimated at around 30% [20, 21]. The causes of anemia are multifactorial [22], but our findings suggest that iron deficiency may be an important contributor to anemia among the girls. The island is not far from the capital, Jakarta, and it would be surprising if the high prevalence of iron deficiency might be attributable to the poor dietary intake of iron, but this should nevertheless be explored. Even though the hepcidin concentration was not significantly higher in the anemic group compared with the non-anemia group at the end of iron supplementation, it is also notable that 43.4% (n = 36) of the subjects were still iron deficient and 38.6% showed evidence of subclinical inflammation. We have no records of morbidity during iron supplementation, but subclinical infections during the study may have limited iron absorption. Evidence from women with asymptomatic malaria has shown that subclinical inflammation can reduce iron absorption by up to 40% [23].

TABLE 4. Hemoglobin, change in hemoglobin, and hepcidin concentration in iron-deficient and iron-replete groups[a]

Variable	Iron deficient[b] (n = 36)	Iron replete (n = 23)	p
Hemoglobin at endline (g/dL)	11.0 ± 1.5	13.1 ± 1.2	< .001
Change in hemoglobin (g/dL)	0.3 ± 1.0	2.5 ± 1.6	< .001
Hepcidin (ng/mL)	39.3 ± 13.5	45.2 ± 20	.218

a. Mean ± SD, independent-sample t-test; difference considered significant at $p < .05$.
b. Iron deficiency defined as serum ferritin < 15 µg/L.

Previous studies showed a positive association between iron supplementation and hepcidin concentration [24, 25]. Berglund et al. suggested that serum ferritin, a marker of iron stor can predict hepcidin concentration and proposed hepcidin as a potential iron status indicator for infants [24]. In line with previous findings [24, 26, 27], hepcidin concentrations tended to be lower among iron-deficient than non-iron-deficient subjects (**table 3**). Although the result was not statistically significa in our study, probably due to the small sample size, the difference in hepcidin concentration between iron-deficient and non-iron-deficient subjects was comparable with that found in a previous study of US female soldiers [28]. In that study, labeled iron supplements were given to healthy young women, and no association was found between hepcidin and iron status indicators, even though there was a significant inverse association between hepcidin concentration and iron absorption. In addition, log hepcidin concentrations were significantly associated with log CRP concentrations. It is important to note, however, that the majority of these women were iron replete, whereas more than one-third of the Indonesian girls were still anemic. Furthermore, only 10% of the American women in that study showed evidence of inflammation, compared with almost 40% of the Indonesian girls. The presence of subclinical inflammation in the apparently healthy Indonesian adolescent girls indicates higher exposure to infections in the environment or poorer immunological development, or both, compared with the American women. Whatever the reason, subclinical inflammation during the study may have impaired the Indonesian girls' responses to the iron supplement.

We found no significant association between hepcidin and hemoglobin, a result that was in line with findings from Bangladeshi women [26]. A previous study showed that hemoglobin and MCV were not associated with serum hepcidin at 12 weeks of iron supplementation, but the associations became significant at 6 months of supplementation [24]. That study was conducted on low-birthweight infants, and different sages of iron supplements were given to investigate the association of hepcidin and iron status indicators. The present study was conducted at the end of 12 weeks of iron supplementation; the short duration may be the reason that we did not find any association between hepcidin and iron status indicators, red cell parameters, and markers of inflammation. On the one hand, similar to our findings, studies among healthy young women showed no association between hepcidin and iron status indicators, although hepcidin was associated with the inflammatory marker CRP [28, 29]. On the other hand, stronger correlations between hepcidin and serum ferritin were reported in other studies on subjects with better baseline iron status than those in our study and the Bangladesh study [23, 30]. We therefore hypothesize that hepcidin better reflects iron status in iron-replete than in iron-deficient subjects, a hypothesis that should be further explored.

The prevalence of subclinical inflammation among the Indonesian girls was 38.6%, but neither of the two acute phase proteins, CRP and AGP, was associated with serum hepcidin concentration. In the study of pregnant women in Bangladesh, a modest association of AGP, but not of CRP, with urinary hepcidin was reported [26]. Although the correlation between hepcidin and AGP in our study was not significant ($r = 0.19$, $p = .16$), the correlation was close to that found in a study of a much larger number ($n = 190$) of Bangladeshi women ($r = 0.20$, $p = .01$). The prevalence of subclinical inflammation in the present study was relatively high compared with that in adolescent girls in Myanmar, where only about 7% had subclinical inflammation [31]. However, the prevalence of subclinical inflammation in the Indonesian girls was similar to that found in younger age groups, where higher rates of subclinical inflammation are reported [32, 33]. The prevalence of inflammation in younger subjects is frequently greater than that in adults [5, 6], and several studies have shown that subclinical inflammation or elevated acute phase protein was associated with higher prevalence rates of anemia among children under 5 years of age in Cambodia, Papua New Guinea, and Nicaragua [32–34]. It is interesting to note that the subclinical inflammation in the Indonesian girls was more typical of chronic inflammation than acute inflammation, since there were 29 girls with elevated AGP (35%) and only 4 (5%) with elevated CRP concentrations. The small number with elevated CRP prevented us from calculating internal correction factors to adjust ferritin for subclinical inflammation, and therefore we used published correction factors. After correction, the prevalence of iron deficiency increased from 39.8% to 43.4%.

Interpretation of the results of this study is limited by the fact t it was cross sectional and could not indicate how subclinical inflammation might have affected the girls' response to iron supplementation. We had no record of morbidity occurring during the study and can only suspect that the high prevalence of subclinical inflammation at the end influenced the response to the iron supplements. Twelve we of iron supplementation may have been too short to reveal any significant associations between hepcidin and either anemia or ferritin concentration. Alternatively, hepcidin data were not available for all subjects, which could have limited the statistical power to detect any difference or association. Last, we had no information on other micronutrient deficiencies or hemoglobinopathies that could contribute to the anemia in the adolescent girls in the present study. It might not have been possible to eliminate all the anemia with iron supplements alone.

In conclusion, we report serum hepcidin concentrations among healthy adolescent girls at the

end of 12 weeks of iron supplementation. Our findings suggest that during the intervention, hepcidin concentrations may have been higher among those who responded poorly to iron supplementation as a consequence of increased subclinical inflammation, which impaired the subjects' responses to the iron supplement. A longitudinal study should be conducted to explore the role of hepcidin in iron supplementation among apparently healthy anemic subjects, but this should also include investigation of other etiological factors of anemia.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

M. K. Htet, D. Dillon, A. Rosida, and I. Timan designed the research; M. K. Htet, D. Dillon, and A. Rosida conducted the research; M. K. Htet and U. Fahmida analyzed the data; M. K. Htet, U. Fahmida, and D.I. Thurnham wrote the paper; M.K. Htet had primary responsibility for the final content. All authors read and approved the final manuscript.

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