



Original Article

Iron status and hepcidin levels as potential regulators of haemoglobin homeostasis in overweight and obese women of childbearing age

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Received 10 May 2019; revised 5 August 2019; accepted 14 August 2019 Available online 7 November 2019



المخلص

أهداف البحث: تعتبر زيادة الوزن من عوامل الخطورة للإصابة بفقر الدم. ولا تزال آليات الربط بين فقر الدم وزيادة الوزن والسمنة غير واضحة. تُحل هذه الدراسة العلاقة بين حالة الحديد (نسبة مستقبلات ترانسفيرين القابلة للذوبان إلى لوغارثم الفيريتين)، وكلا من الهبيدين والهيموجلوبين في النساء السمان وذوات الوزن الزائد ممن هن في سن الإنجاب.

طرق البحث: في هذه الدراسة المستعرضة، قمنا باستقطاب 66 امرأة تتراوح أعمارهن بين 20-29 عاماً مع مؤشر كتلة الجسم <math>23 < /math> كجم / م². وقمنا بجمع بيانات حول الموافقة المستنيرة، وجمع بيانات الهوية، والاستبانة، والقياسات البشرية والمخبرية. ثم تم إجراء اختبار ارتباط سبيرمان لتحديد ارتباط حالة الحديد والهبيدين مع الهيموجلوبين.

النتائج: أظهرت الدراسة مستويات فيريتين 10.2 ± 8.12 نانوغرام / مل، وقيم مستقبلات ترانسفيرين القابلة للذوبان 22.2 ± 7.96 نانوغرام / مل، ونسبة مستقبلات ترانسفيرين القابلة للذوبان إلى لوغارثم الفيريتين 29.3 ± 17.65 نانومول / لتر، بينما كان مستوى الهبيدين 9.0 ± 3.05 نانوغرام / مل. وكان لما مجموعه 75.8% من الخاضعات للدراسة، مستويات فيريتين منخفضة، وقيم مستقبلات ترانسفيرين القابلة للذوبان عالية (51.5%) ونسب مستقبلات ترانسفيرين القابلة للذوبان إلى لوغارثم الفيريتين عالية (87.9%). تتناسب قيم مستقبلات ترانسفيرين القابلة للذوبان وقيم نسب مستقبلات ترانسفيرين القابلة للذوبان إلى لوغارثم الفيريتين بصورة سلبية مع الهيموجلوبين. ولم يكن هناك ارتباط بين مستوى الهبيدين والهيموجلوبين. كما كان هناك ارتباط إيجابي بين الفيريتين مع الهيموجلوبين.

الاستنتاجات: أظهرت هذه الدراسة ارتباط حالة الحديد بالهيموجلوبين لدى النساء السمان وذوات الوزن الزائد في سن الإنجاب. جميع النساء كنّ يكوّن الكريات الحمراء مع فقر الدم بسبب نقص الحديد. نوصي النساء السمان وذوات الوزن الزائد بإجراء المزيد من التحاليل المخبرية للكشف عن فقر الدم المبكر. نشجع استهلاك الأطعمة التي تعزز امتصاص الحديد مثل حمض الأسكوربيك.

الكلمات المفتاحية: فقر الدم؛ الهبيدين؛ الالتهاب؛ السمنة؛ ونسبة مستقبلات ترانسفيرين القابلة للذوبان إلى لوغارثم الفيريتين

Abstract

Objectives: Overweight is considered a risk factor for anaemia. However, the mechanisms underlying anaemia development in overweight and obese people remain unclear. This study analysed the correlation of iron status (soluble transferrin receptor [sTfR]/log ferritin ratio) and hepcidin levels with haemoglobin (Hb) levels in overweight and obese women of childbearing age.

Methods: In this cross-sectional study, we recruited 66 women aged 20–29 years with a body mass index ≥ 23 kg/m². We gathered data on informed consent, demographic characteristics, questionnaire responses, anthropometric and laboratory values. A Spearman correlation test was performed to determine the correlation.

Results: The mean levels of ferritin and sTfR were 10.2 ± 8.12 and 22.2 ± 7.96 ng/ml, respectively, and the mean sTfR/log ferritin ratio was 29.3 ± 17.65 nmol/L. The mean hepcidin levels were 9.0 ± 3.05 ng/ml. In total, 75.8% of subjects had low ferritin levels, high sTfR (51.5%) levels, and a high sTfR/log ferritin ratio (87.9%). The sTfR levels ($r = -0.359$; $p = 0.003$) and sTfR/log ferritin ratio ($r = -0.375$; $p = 0.002$) were negatively

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Peer review under responsibility of Taibah University.



correlated with Hb levels. There was no correlation between the levels of hepcidin and Hb ($r = -0.140$; $p = 0.264$), but there was a positive correlation between ferritin and Hb levels ($r = 0.350$; $p = 0.004$).

Conclusion: This study showed a correlation between iron status and Hb levels in overweight and obese women of childbearing age. All the women had erythropoiesis with iron deficiency anaemia. We recommend that overweight and obese women undergo further iron parameters for the detection of early anaemia. In this group, the consumption of foods that enhance iron absorption, such as ascorbic acid, should be encouraged.

Keywords: Anaemia; Hepcidin; Inflammation; Obesity; sTfR/log ferritin ratio

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Introduction

Anaemia has become an epidemic and is a major global health problem that results in decreased quality of life and work capacity. According to the World Health Organization (WHO), nearly 2 billion people worldwide have anaemia. The most common cause of anaemia is iron deficiency, followed certain chronic diseases that cause anaemia, especially in developing countries where infection rates are still high. The global prevalence of iron deficiency anaemia was 75–80%, and that of anaemia due to chronic diseases was 23–50%.¹ In Indonesia, at 2013 the prevalence of iron deficiency anaemia in patients over the age of 1 year was 21.7%, and this prevalence was higher in women than in men.² Women's health, especially during childbearing years, is important for reproductive processes, pregnancy preparedness, childbirth, and breastfeeding. Hence, further investigation is needed to determine the causes of anaemia in this group. In particular, chronic inflammation, such as that noted in obesity, can cause anaemia.³

WHO estimates that more than 1 billion adults worldwide are overweight, while 300 million people are obese.⁴ Additionally, women have a higher percentage of body fat on average than men. Data from Basic Health Research 2013 in Indonesia showed that the prevalence of obesity in adult women >18 years was 32.9% and that in adult males was 19.7%, while the prevalence of central obesity was 26.6%.²

Obesity is caused by excessive energy and nutrient intake. Several studies have shown that increases in adipose tissue result in low availability of serum iron and lead to limited iron absorption from the duodenum.⁵ The mechanism underlying anaemia development in individuals with obesity is still unclear. Recent research on obesity has focused on inflammation because not only is adipose tissue

an energy reserve,⁵ but it also triggers oxidative stress and the production of proinflammatory cytokines that cause mild systemic inflammation, especially in cases of central obesity.⁶ Inflammation causes an increase in hepcidin levels, which inhibits iron release from cells.⁶ Hepcidin is a primary antimicrobial peptide hormone regulating systemic iron metabolism. Studies in premenopausal women with obesity have shown that inflammation has a greater effect on hepcidin than do serum iron levels.⁶

A diagnosis of iron deficiency anaemia can be made based on several parameters, including serum iron levels, an indicator of iron content; ferritin levels, an indicator of iron reserves; and the soluble transferrin receptor (sTfR)/log ferritin ratio.⁷ In developing countries, the prevalence of obesity is increasing, while the prevalence of anaemia remains high, making it is necessary to identify the causes of anaemia in obese people in order to develop appropriate management strategies. There are few studies linking obesity with anaemia through several parameters, although these are limited. Therefore, the present study aimed to analyse the correlation of iron status (sTfR/log ferritin ratio) and hepcidin levels with haemoglobin (Hb) levels in overweight and obese women of childbearing age (WCA).

Materials and Methods

Subjects and study design

This was a cross-sectional study conducted among WCA. Subjects answered a questionnaire and underwent anthropometric and laboratory examinations in the form of routine blood tests, iron status (ferritin and sTfR) tests, and tests for hepcidin levels. Written informed consent was obtained from all subjects. Sample size was calculated using a formula, considering that a correlation was to be detected, with a power of 95% and an α -level of 0.05.

The subjects were chosen by consecutive sampling based on inclusion and exclusion criteria. Inclusion criteria: WCA aged 20–29 years, body mass index (BMI) ≥ 23 kg/m², never married, and not menstruating. Exclusion criteria: previous or current history of cardiovascular, liver, gastrointestinal, hormonal disorders, infectious, or chronic diseases; routine consumption of alcohol; under treatment with hormonal drugs (oestrogen or testosterone); and taking vitamin C and iron supplements.

Examination and questionnaire

Anthropometric examination consisted of examinations for weight, height, and BMI calculated using a formula (weight in kilogram divided by height in meter squared).⁸ The sTfR/log ferritin ratio was calculated by comparing the sTfR levels and the log of the ferritin levels.⁹ The Asia–Pacific BMI classification was used, and the categories were as follows: overweight, BMI 23–24.9 kg/m²; obese category 1, BMI 25–29.9 kg/m²; obese category 2, BMI ≥ 30 kg/m²; and obese category 3 (morbidly obese), BMI ≥ 40 kg/m².^{8,10,11} The questionnaire gathered personal information, such as age, education, and occupation.

Questions on medical history, in order to determine whether participants met any medical history-related exclusion criteria, and diet pattern, to identify the dietary factors that enhance or inhibit iron absorption, were also included. Laboratory analyses were performed using the Quantikine IVD human sTfR immunoassay and ferritin enzyme immunoassay no. 4S00058 reagents. The examination of sTfR, ferritin, and hepcidin was carried out according to the instructions provided in the ELISA kit.

The Quantikine IVD human sTfR immunoassay employs the quantitative sandwich enzyme immunoassay technique. The product contains a microplate pre-coated with a monoclonal antibody specific to human hepcidin. Standards and samples are pipetted into the wells of the plate, and any hepcidin present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific to human hepcidin is added to the wells. Following a wash to remove any unbound antibody–enzyme reagent, a substrate solution is added to the wells and colour develops in proportion to the amount of hepcidin bound in the initial step. The colour development is stopped, and the intensity of the colour is measured.

To initiate the ferritin enzyme immunoassay procedure after the washing step, the enzyme substrate was added. The enzymatic reaction was terminated by the addition of the stop solution. The absorbance was measured using a microtiter plate reader. The intensity of the colour formed by the enzymatic reaction was directly proportional to the concentration of ferritin in the sample. A set of standards was used to plot a standard curve from which the amount of ferritin in patient samples and controls could be directly read.

Statistical analysis

Data was analysed using computer software. Data normality was tested using the Kolmogorov–Smirnov test. Ferritin, hepcidin, and sTfR levels and the sTfR/log ferritin ratios were not normally distributed; hence, transformation was carried out. However, the data continued to not show a normal distribution even after transformation. Hence, the Spearman test was used for analysis. The Spearman correlation test was conducted to determine the relationship of iron status (sTfR/log ferritin ratio) and hepcidin levels with Hb levels.

Results

Characteristic subjects

Table 1 presents the subjects' anthropometric characteristics. The mean age was 20 ± 3.9 years, and all subjects had excessive weight, with the majority having a BMI included in obese categories 1 (43.9%) or 2 (43.9%). All subjects were college students. Moreover, 90.9% of subjects had a waist circumference higher than the reference value, and the waist-to-hip ratio (WHR) of all subjects was higher than the reference (>0.7 cm).

An evaluation of factors that could affect iron and hepcidin levels is presented in Table 2. Most subjects consumed food containing vitamin C weekly and had a

Table 2: Factors affecting hepcidin and iron.

Parameter (n = 66)	Frequency	Percentage (%)
Consuming foods containing every week		
Yes	52	77,6
No	14	20,9
Consuming foods containing iron		
Yes	58	87,8
No	8	11,9
Consuming tea or coffee		
Yes	43	65,1
No	23	34,3
Consuming alcohol		
Yes	3	4,5
No	63	94
Smoking		
Yes	1	1,5
No	65	97
History of obesity		
<18 years	48	70,6
>18 years	18	26,5
Menstrual regularity		
Regular	43	64,2
Irregular	23	34,3
Physical activity		
Sedentary	51	77,27
Active	15	22,72

Table 1: Anthropometry characteristics.

Parameter	Percentage (%)	Average \pm Standard deviation	min; max	Reference value
Height (cm)		157.4 ± 5.32	145–168	
Weight (kg)		76.4 ± 13.49	54.4–123.0	
Body mass index (kg/m^2)		30.7 ± 5.09	23.2–50.5	18–23.0
Overweight	10.7	24.05 ± 0.86	23.26–25.38	23–24.9
Obese		31.34 ± 4.91	25.38–50.55	
Category 1	43.9			25–29.9
Category 2	43.9			≥ 30
Category 3 (morbid)	1.5			≥ 40
Waist circumference (cm)		92.2 ± 11.90	68.5–137	<80
<80	9.1			
>80	90.9			
Waist size (cm)		106.7 ± 12.23	57.0–143	
Waist hip ratio (cm)		0.8 ± 0.08	0.7–1.3	<0.7
<70	9.1			
>70	90.9			

Table 3: Laboratory examination results.

Parameter	average \pm standard deviation	min; max	Reference value
Hemoglobin (g/dL)	12.9 \pm 1.17	10–15.2	11.7–15.5
Hematocrit (%)	38.9 \pm 3.14	31.1–45.7	35–47
Erythrocytes (106/ μ L)	4.7 \pm 0.41	3.5–5.57	3.8–5.2
MCV (fL)	82.1 \pm 5.12	68.4–95.5	80–100
MCH (pg)	27.3 \pm 1.96	21.8–31.9	26–34
MCHC (g/dL)	33.3 \pm 0.95	31.4–36.2	32–36
Leukocytes (103/ μ L)	8.8 \pm 2.46	4.5–18	3.6–11
Calculate total lymphocytes (sel/mm ³)	2689.5 \pm 726.29	1178–4841.6	800–1050
eLFG (mL/mnt/1,73 m ²)	121.7 \pm 12.39	78–144	>60
Hepcidin (ng/ml)	9.0 \pm 3.05	3–19.1	18
sTfR (ng/ml)	22.2 \pm 7.96	11.9–50.2	21
Ferritin (ng/ml)	10.2 \pm 8.12	2.1–41.5	15
Ratio sTfR/log ferritin (nmol/L)	29.3 \pm 17.65	9.3–84.5	14
GDP (mg/dL)	82.1 \pm 14.42	66–157.0	<100

Table 4: Percentage of iron deficiency based on ferritin, sTfR, and ferritin sTfR/log ratio.

Ferritin		sTfR				ratio sTfR/log ferritin					
low		high		low		high		low		high	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
50	(75.8)	16	(24.2)	32	(48.5)	34	(51.5)	8	(12.1)	58	(87.9)

sedentary physical activity level. While 71.6% of subjects consumed food containing iron every day, 22.4% consumed food that inhibits iron absorption. Laboratory blood test results (Table 3) with a mean Hb level of 12.9 \pm 1.1 g/dL, and 18.1% of subjects had low Hb levels. The levels of hepcidin and ferritin in all subjects were lower than the reference value, whereas the sTfR levels and sTfR/log ferritin ratios were higher (see Table 4).

Iron status

In this study, the cut-off point for ferritin levels was 15 ng/ml; for sTfR levels, > 21 nmol/L; and for the sTfR/log ferritin ratio, > 14. In total, 75.8% of subjects had low ferritin levels and 87.9% had a high sTfR/log ferritin ratio.

Correlation of iron status and hepcidin levels with Hb levels

Table 5 presents the correlation of iron status and hepcidin levels with Hb levels. sTfR levels and sTfR/log

ferritin ratios showed negative correlations with Hb levels, while ferritin levels showed a positive correlation and hepcidin levels showed no correlation.

Discussion

In the present study, most subjects were in the pre-obese or obese 1 category, having above-average WHRs. Changes in body weight are associated with changes in fat distribution that differ by sex, parity, race, ethnicity, and age.^{12,13} Increases in adipose are known to result in limited iron absorption and low iron availability.^{5,13} Tussing-Humphreys et al. (2010) showed that overweight adolescent girls were at risk of iron deficiency, and inflammatory processes were suspected to be involved.¹⁴ Choma et al. (2015) showed that BMI and abdominal circumference were correlated with serum iron and transferrin levels and Hb and ferritin saturation. BMI is correlated with low serum iron and ferritin levels.¹⁵ Yanoff et al. (2007) showed that obese subjects had lower serum iron levels and higher transferrin receptor levels than did people of average weight.¹⁶

In this study, the examination of iron status in the subjects revealed iron deficiency anaemia, reflected by low levels of hepcidin and ferritin, and increased sTfR levels. A significant decrease in hepcidin levels followed by a decrease in ferritin levels is an early sign of iron deficiency anaemias.^{17,18} Low levels of ferritin are indicative of decreased iron stores, whereas high sTfR levels indicate an increase in the iron requirement for erythropoiesis.^{17,18} An examination of the sTfR/log ferritin ratio is a more accurate method for distinguishing iron deficiency anaemia from anaemia due to inflammation or mixed anaemia.^{17,18}

In this study, sTfR levels and the sTfR/log ferritin ratio showed a negative correlation with Hb levels, which —

Table 5: Results of correlation of iron status and hepcidine with hemoglobin.

Variable	Hemoglobin		Information
	r	P	
Ratio sTfR/log ferritin	-0.375	0.002 ^a	Meaningful, negative, very weak
Hepcidin	-0.140	0.264	Meaningless
sTfR	-0.359	0.003 ^a	Meaningful, negative, very weak
Ferritin	0.350	0.004 ^a	Meaningful, positive, very weak

^a Correlation is significant if p < 0.05.

although weak — was statistically significant. This shows that if the sTfR level and sTfR/log ferritin ratio are higher, the Hb level is lower. Ferritin levels showed a positive correlation with Hb levels, which was statistically significant despite being very weak. This implies that the lower the ferritin level, the lower the Hb level; however, Hb examination showed that 18.1% of subjects experienced anaemia. The results showed that stage II iron deficiency anaemia (iron deficiency erythropoiesis) was reflected by decreased ferritin levels, increased sTfR levels, and an increased sTfR/log ferritin ratio, despite the presence of normal Hb levels. In this phase, there was a decrease in iron deposits and erythropoiesis disruption had started, but the production of Hb was unaffected.¹⁹ Gibson et al. (2014) showed that BMI is a positive predictor of log sTfR, ferritin, and leptin, but not of log hepcidin or IL-6 levels.²⁰ A BMI range that is too wide (BMI range 23.2–50.5 kg/m²) could lead to the observation of a weak correlation.

The combination of several iron status parameters can improve the classification accuracy of anaemia diagnosis, especially in cases of anaemia accompanied by active inflammation.¹⁸ The results of the present study indicate that the detection of iron deficiency anaemia was 75.8% when only the ferritin examination was used, but when all three parameters (ferritin levels, sTfR levels, and the sTfR/log ferritin ratio) were used, the detection increased to 87.9%. The multicentre study by Skikne et al. (2011) demonstrated an improvement in the detection of iron deficiency anaemia with the use of three parameters. The detection rate was 41% when only the ferritin examination was used, and increased to 92% when three parameters were applied. If only the ferritin examination is used, iron deficiency anaemia in subjects with inflammation may become underdiagnosed.¹⁸

Diet affects the increase and inhibition of iron absorption, and it may thus be a cause of anemia.^{21,22} In the present study, an evaluation was conducted to identify nutritional intake that can increase or inhibit iron absorption. Diet contributes to iron deficiency, which leads to iron deficiency anaemia. A diet full of food items containing iron with high bioavailability (20–30% absorbed), such as red meat, and foods that increase absorption, such as ascorbic acid, may prevent iron deficiency anaemia.²¹ Heme iron absorption is less affected by the body's iron status and is not affected by other constituents. Non-heme iron, like that found in green vegetables, has low bioavailability; in the intestinal lumen, it is released and chelated quickly by other constituents in the food.^{21,23,24} The present study only evaluated the quantity of food containing iron and vitamin C, and the questionnaire only assessed daily and weekly intake frequency. The present study did not distinguish between the types of foods that contain iron and vitamin C.

Menstrual data and a history of obesity are used to describe hormonal conditions and long-standing obesity associated with chronic inflammation. Most subjects in the present study had been obese since childhood (<18 years). Oestrogen is responsible for the growth of the endometrial layer. Oestrogen is also produced by adipocytes. Hence, in

obese women, more oestrogen is produced, resulting in a thicker endometrial layer that results in menorrhagia²⁵ — a condition of heavy menstrual bleeding of longer duration that can lead to iron deficiency anaemia.^{13,26} Bernardi et al. (2016) showed that 68.2% of premenopausal women with menorrhagia experience iron deficiency and 18.2% experience anaemia.²⁷ However, this study only evaluated the regularity of the menstrual cycle and did not calculate the quantity of blood loss during menstruation.

Obesity results in chronic inflammation that can increase the levels of hepcidin, which can then bind to ferroportin, inhibit iron absorption, and release iron from cells, preventing iron from entering plasma.^{6,28,29} The present study found contradictory results, showing that ferritin levels were normal or even low and were accompanied by low levels of hepcidin in obese individuals. Hepcidin levels showed a negative correlation with Hb levels, although this was not statistically significant. If hepcidin levels increase, iron cannot enter the plasma, and consequently, Hb levels decrease.^{30,9,31} In the present study, hepcidin levels in the participants were normal or lower than normal. The lack of correlations of hepcidin levels with Hb levels could be caused by the duration of obesity, wide range of BMI, and protective effects of oestrogen.^{30,9,31} Siddique et al. (2014) showed that patients with non-alcoholic fatty liver had iron deficiency, and this was associated with female sex, African ancestry, and increased BMI. In previous studies, low levels of hepcidin were found in obese subjects with iron deficiency.^{30,9,31}

Regarding duration of obesity, about 70.6% of subjects in our study had been obese since they were children; hence, it is estimated that the subjects had been obese for more than five years. Factors such as the degree of obesity and duration of obesity affect the stimulation of hepcidin release.³² Hypoxia, anaemia, increased erythropoiesis, and decreased iron stores inhibit the expression of hepcidin^{28,33}. Ridha et al. (2014) showed that in children with obesity, inflammation was present, although there was no increase in hepcidin levels. In this study, only four subjects in the morbid obesity category showed normal or low ferritin and hepcidin levels. This may be because the intensity of stimulation and the duration of inflammatory exposure was not enough to stimulate hepcidin release.³² Lisa et al. (2009) shows that serum hepcidin levels are elevated in obese women despite iron depletion, suggesting that they respond to inflammation rather than iron status. Inflammation may perpetuate this condition through the hepcidin-mediated inhibition of iron absorption.⁷ A preliminary study suggested that body fat affects prohepcidin concentration and thereby affects iron haemostasis.³⁴ In childhood, obesity increases hepcidin levels and is associated with a diminished response to oral iron therapy in cases of iron deficiency anaemia.³⁵

Oestrogen has protective effects against increasing hepcidin levels.²⁶ High oestradiol levels triggered by gonadotropins cause the suppression of serum hepcidin levels.²⁶ In this study, oestrogen examination was not carried out, and only the regularity of the subjects' menstrual cycles was evaluated. Lehtihet et al.'s (2016)

cohort study showed that women with normal menstrual cycles had low levels of hepcidin²⁶. Angeli et al. (2016) showed that iron status varies during the menstrual cycle, and this should thus be considered when using hepcidin as a diagnostic measure for WCA.³⁶ In the present study, 43 (64.2%) subjects claimed that they had regular menstrual cycles.

The limitations of the present study were related to costs and deadlines for conducting research. Not all variables were analysed, there was no comparison with a control group, and the sample size was small. Further research needs to be conducted through comparisons between people of normal weight and those with a higher degree of obesity to gain further information about iron status and the inflammation caused by obesity. In addition, it is necessary to further examine the factors that influence the development of iron deficiency in conjunction with obesity.

Conclusion

There was a correlation between iron status and Hb levels in overweight and obese WCA. The iron status results indicated that the subjects had erythropoiesis iron deficiency anaemia. However, there was no correlation between hepcidin and Hb levels in overweight or obese WCA. This could be due to the duration of obesity in the subjects, the wide BMI range, and the protective effects of oestrogen. We recommend that overweight and obese women undergo further laboratory tests for anaemia to enable early detection, in addition to consuming foods that enhance iron absorption, such as ascorbic acid, and limiting foods that inhibit iron absorption.

Source of funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The Ethics Committee of Medical Faculty Diponegoro University West Java Indonesia approved the study design and the consent procedure (approval number 984).

Authors contributions

All authors have critically reviewed and approved the final version of the manuscript. DAI, HWS, and MH conceived and designed the study, conducted research, provided research materials, and collected and organized data. DAI analysed and interpreted the data. DAI, HWS, and MH wrote the initial and final drafts of this article. All authors have critically reviewed and approved the final

draft and are responsible for the content and similarity index of the manuscript.

Acknowledgment

We thank Fatimah Muis and Darmono SS, staff of the clinical nutrition specialist educational program in the Medical Faculty of Diponegoro University, Semarang, Central Java Indonesia who collaborated with us during this study.

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How to cite this article: Insani DA, Subagio HW, Hendrianingtyas M. Iron status and hepcidin levels as potential regulators of haemoglobin homeostasis in overweight and obese women of childbearing age. *J Taibah Univ Med Sc* **2019**;14(6):531–537.