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Research article

Hepcidin and iron metabolism in preterm infants

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Abstract: Background: Iron deficiency (ID) and ID anemia are widespread in low-income countries, particularly among preterm infants. Hepcidin is a key regulator of iron metabolism, which offers the possibility of new solutions to diagnose ID in premature infants. Objective: To explore the relationship between iron metabolism and hepcidin in premature infants. Materials and methods: The study involved 81 preterm infants between 28^{+1} and 36^{+6} who underwent iron status indicators and hepcidin testing at 6 months of corrected gestational age. The preterm infants were divided into two groups based on iron status indicators: ID and no ID. Results: Serum hepcidin was lower for premature infants with ID compared to those without ID ($\log_{10}$hepcidin, 1.18 ± 0.44 vs 1.49 ± 0.37, p = 0.002). A single-variate linear regression model was used to explore the correlation between hepcidin and other indicators of iron metabolism. A strongly positive relationship was observed between hepcidin levels and ferritin levels ($p < 0.001$) in the correlation analysis. Conclusions: Hepcidin can be used as an efficient indicator of iron storage and a promising indicator for the early diagnosis of ID in premature infants.

Keywords: hepcidin; iron deficiency; iron deficiency anemia; iron metabolism; preterm infants

1. Introduction

Iron deficiency anemia (IDA) is the most common nutritional deficiency disease, which affects more than 1.2 billion people worldwide [1]. Preterm infants are more likely to develop iron

deficiency (ID) and IDA [2] early due to inadequate iron stores [3,4]. Eighty percent of iron transfer from mother to fetus occurs during the third trimester of pregnancy. Preterm infants have a significantly higher prevalence of IDA than full-term infants due to exclusive breastfeeding [4], frequent infections [4], postnatal catch-up growth [2] and medically induced blood loss [3]. Therefore, preterm infants are at particular risk for ID, and the incidences of ID and IDA in early preterm (28–32 weeks) and term infants were 48% and 26.5% [5], 29.1% and 17.9% [6], respectively.

Iron is involved in the synthesis of neuronal myelin sheaths, the transmission of dopamine neurotransmitters, the metabolism of neurons and the synthesis of several enzymes in brain tissue. Evidence is clear that early infancy ID is a strong risk factor for ID in later infancy [7] and can lead to long-term, irreversible deficits in cognition, motor function, hearing, vision and behavior [8–11]. ID-induced brain damage persists even after ID has been corrected [12].

Therefore, efforts are needed to prevent, diagnose or promptly treat iron deficiency in preterm infants. However, little is known about the mechanisms regulating iron homeostasis in preterm infants, especially in very small preterm infants [13]. There is still a lack of uniform and highly accurate indicators to assess iron status in preterm infants [14].

Hepcidin is a negative regulator of iron homeostasis [15]. Hepcidin inhibits iron absorption and reuse by binding to ferroportins, causing ubiquitination, internalization and degradation of ferroportins, resulting in decreased dietary iron uptake, increased iron recycling by macrophages and iron storage by hepatocytes [15,16]. Recent studies have demonstrated that hepcidin is considerably more sensitive and specific than serum iron, ferritin, transferrin saturation and total iron binding for the diagnosis of ID and IDA [17–19]. Hepcidin in preterm infants is affected by the maternal iron metabolism level, intrauterine hypoxia, inflammation and other factors [20]. There are few relevant studies about the relationship between hepcidin and iron metabolism in preterm infants and its value in the diagnosis of ID in preterm infants.

This study focuses on identifying levels of hepcidin in premature infants and the relationship between iron metabolism and hepcidin in premature infants.

2. Materials and methods

2.1. Ethical considerations

The investigation had the approval of the Ethics Review Committee of the Second West China Hospital of Sichuan University (Medical Research 2019 Approval No. (086). Participation in the survey was subject to free and informed written consent from the parental unit of the participants. After learning more about the study protocol, parents of preterm infants were free to decline or withdraw from the study at any time.

2.2. Study population and setting

The study was conducted from January 1, 2020 to June 31, 2020, at the Department of Child Health, West China Second University Hospital.

2.3. Sample

This prospective study included 81 preterm infants between 28^{+1} and 36^{+6}. The preterm infants included in the study were divided into two groups: ID and no ID. Diagnostic criteria for ID: ID was defined as SF < 12 μg/L and CRP < 5 mg/L, or SF < 30 μg/L and CRP ≥ 5 mg/L [21]. All preterm infants undergoing child health care were included in this study from January 1, 2020 to June 31, 2020. Preterm infants with non-IDA, gastrointestinal diseases, active bleeding, severe infections, severe cardiovascular diseases, cerebrovascular diseases, liver diseases, kidney diseases, neuropsychiatric diseases or genetic metabolic diseases were excluded from the study.

2.4. Information collected

A standardized form was completed for each case, including birth information (birth weight, birth length, birth head circumference, sex, mode of delivery and neonatal comorbidities), maternal information (age, gestational comorbidities, iron supplementation during pregnancy, blood transfusion during pregnancy and routine blood results at delivery) and infant's 24-hour diet (i.e., the amount of breast milk or formula, breast milk fortification, complementary foods and other infant foods).

Venous blood specimens were collected at 6 months of corrected gestational age, which were treated with ethylenediaminetetraacetic acid and sent to the laboratory of West China Second University Hospital for the detection of hemoglobin (HGB, XN-9000 Automatic Blood Counting Instrument and Instrument Supporting Reagent Kit, Sysmex, Japan), mean corpuscular volume (MCV, XN-9000 automatic blood counting instrument and instrument supporting reagent kit, Sulfated hemoglobin spectrophotometry, Sysmex, Japan), mean corpuscular hemoglobin volume (MCH, XN-9000 automatic blood counting instrument and instrument supporting reagent kit, Sulfated hemoglobin spectrophotometry, Sysmex, Japan), mean corpuscular hemoglobin concentration (MCHC, XN-9000 automatic blood counting instrument and instrument supporting reagent kit, Sulfated hemoglobin spectrophotometry, Sysmex, Japan), serum iron (SI, ADVIA XPT automatic biochemical analyzer and instrument supporting reagents, Ferrozine method, Siemens, Germany), ferritin (SF, CENTAUR XPT fully automated chemiluminescence analyzer and supporting kits, Siemens, Germany), transferrin saturation (TS, calculation based on SI and TIBC), total iron binding capacity (TIBC, ADVIA XPT automatic biochemical analyzer and instrument supporting reagents, Chemiluminescence, Immunoturbidimetry, Siemens, Germany) and C-reactive protein. The same samples were also sent to the laboratory of Sichuan University Research Institute for determination of hepcidin levels in preterm infants by using enzyme-linked immunosorbent assay (Hepcidin Elisa; RD; USA).

2.5. Statistical analyses

Data were analyzed using SPSS 23.0 software. Descriptive statistical analysis was performed on the basic characteristics of the study subjects, with measurement data described by the mean ± standard deviation (mean ± SD) and count data described by the composition ratio. The distribution of the basic characteristics between the two groups was tested for differences; the measurement data were described by t-test and the count data by chi-square test or Fisher's exact probability method for differences.

3. Results

Table 1. Basic characteristics of preterm infants according to iron status (ID vs. No ID).

	ID				No ID				
Demographic features	N=23	%	mean	SD	N=58	%	mean	SD	*p* value
Infants									
Gender									
Male	16	69.6			20	34.5			
Female	7	30.4			38	65.5			0.33
Birth weight (g)			1916.3	584.17			2184.55	584.02	0.07
Birth length (cm)			42.3	4.02			43.14	7.17	0.60
Delivery mode									0.78
Vaginal delivery	5	21.7			42	72.4			
Cesarean	18	78.3			16	27.5			0.78
Mothers									
Gravidity			1.43	0.66			1.41	0.5	0.88
Parity			1.52	0.59			1.26	0.52	0.06
Anemia	4	17.4			9	15.5			0.84
Iron supplementation in pregnancy	10	43.5			25	43.1			0.98
Gestational hypertension	1	4.3			4	6.9			0.66

Table 2. Serum hepcidin of preterm infants according to iron status (ID vs. No ID).

	ID		No ID		p value
	mean	standard deviation	mean	standard deviation	
HB (g/L)	104.00	4.24	124.89	9.11	0.002
MCV (fl)	65.15	8.41	77.66	3.40	0.281
MCH (pg)	20.35	2.62	26.00	1.99	<0.001
MCHC (g/L)	313.00	0.001	336.24	10.76	0.003
SI (umol/L）	14.45	5.58	12.00	3.49	0.340
TS (%)	18.15	8.83	20.57	7.00	0.632
TIBC (umol/L)	85.05	8.83	60.02	10.18	0.030
$\log_{10}$ SF (ng/ml)	0.91	0.31	1.43	0.29	0.014
$\log_{10}$ Hepcidin (ng/ml)	1.18	0.44	1.49	0.37	0.002

Note: 1) Hepcidin and SF did not obey normal distribution, so they were log-transformed and tested for differences using an independent samples test; 2) Infants with an elevated C-reactive protein concentration (≥8 mg/L) at any time point were excluded; 3) HB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin volume; MCHC: mean corpuscular hemoglobin concentration; SI: serum iron; SF: ferritin; TS: transferrin saturation; 4) Significantly different between the two groups, $p < 0.05$ (t test).

The demographic features of the study population based on iron status are given in Table 1. There were no significant differences in demographic or clinical parameters across the groups. serum

hepcidin, MCH, MCHC, TIBC and SF were lower for premature infants with ID compared to those without ID (Table 2). Mean serum hepcidin levels were significantly lower in iron-deficient preterm infants than in non-iron-deficient preterm infants (Figure 1). To explore the possibility of predicting the indicator of hepcidin and its association with other iron status indicators in premature infants, univariate linear regression models were used and are presented in Table 3. Univariate regression analysis of hepcidin revealed a strong correlation between hepcidin and ferritin (Table 3). In the present study, we developed univariate regression models for hepcidin; a strongly positive relationship was observed between hepcidin levels and ferritin levels ($p< 0.0001$) in the correlation analysis (Table 3 and Figure 2). No correlation was observed among hepcidin levels and birth weight, birth length, HB, MCH, MCV, SI, SF and TIBC.

Table 3. Univariate regression model predicting hepcidin in preterm infants at 6 months of correction.

Variables N=81	Regression coefficient	Standard error	t value	p value
Birth weight	<0.001	0.000	0.656	0.514
Birth length	-0.003	0.008	0.433	0.666
HB	0.002	0.005	0.399	0.691
MCV	-0.016	0.017	0.939	0.351
MCH	-0.001	0.036	0.034	0.973
MCHC	-0.003	0.006	0.504	0.616
SI	0.018	0.048	0.380	0.705
TS	-0.014	0.028	0.511	0.611
TIBC	-0.015	0.010	1.474	0.145
$\log_{10}$SF	0.704	0.186	3.790	<0.001

Note: 1) Hepcidin and SF did not obey normal distribution, so they were log-transformed and tested for differences using an independent samples test; 2) HB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin volume; MCHC: mean corpuscular hemoglobin concentration; SI: serum iron; SF: ferritin; TS: transferrin saturation.

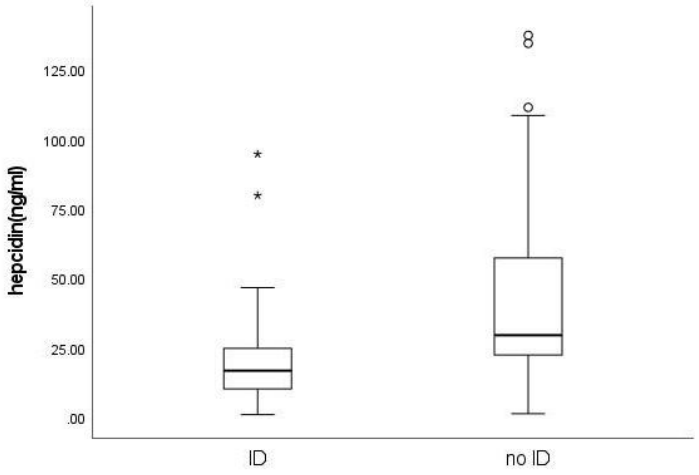

Figure 1. Hepcidin levels in preterm versus normal preterm infants (ID vs. No ID).

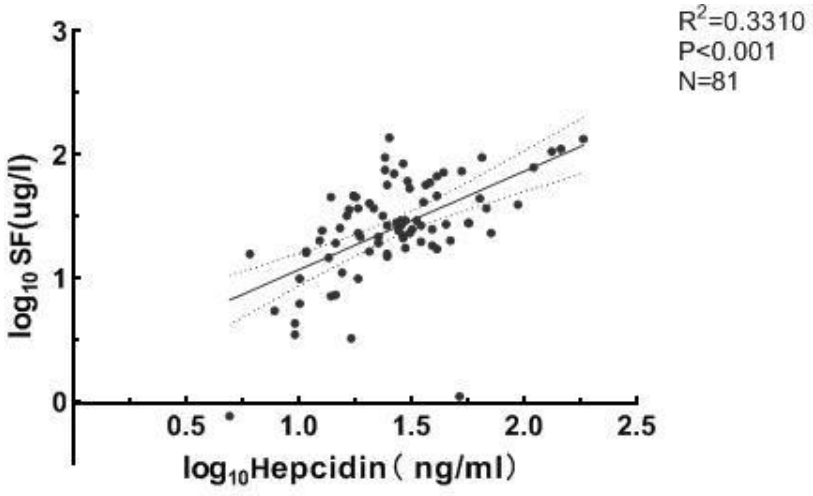

Figure 2. Hepcidin and SF linear regression.

4. Discussion

ID, as we all know, is a major issue for premature infants. Premature infants have an ID rate as high as 48% [5], which has a significant impact on their neurological, motor and physical development. Hepcidin is a core factor in the regulation of iron homeostasis. As early as 2001, Pigeon et al. found that hepcidin expression was increased in iron overload mice [22]. Since then, numerous studies on the connection between hepcidin and iron homeostasis in adults and kids have revealed that hepcidin has higher specificity and sensitivity in the diagnosis of ID and can be used for early diagnosis of ID when compared to ferritin and serum iron [19,23]. Premature infants' iron homeostasis differs significantly from that of adults and children due to insufficient iron storage, catch-up growth, and iatrogenic blood loss [4,5]. Few studies have been done on how hepcidin levels and iron status indices change in premature infants six months after birth.

In the present study, we investigated the correlation between hepcidin and iron status indicators in preterm infants. We discovered that hepcidin may be a good indicator of iron status in premature infants in the absence of infection. Hepcidin levels were substantially lower in preterm infants with ID than in those without ID. This is consistent with the results of previous studies [23–26]. In comparison to newborns with adequate iron status, iron-deficient infants at 6 and 12 months exhibited decreased serum hepcidin concentrations, according to a Spanish research of healthy 1-year-olds [27]. Hepcidin is the primary negative regulator of iron absorption in the small intestine, iron transport across the placenta and iron release from macrophages, according to evidence from transgenic mouse models [28]. Mice with the hepcidin gene deleted develop severe iron overload [26], whereas mice with hepcidin overexpression develop severe anemia [29]. Inadequate iron concentration can be conveyed through the BMP/SMAD signaling pathway, reducing Smad1/5/8 phosphorylation, reducing hepcidin mRNA transcription and inhibiting hepcidin production [30]. Sanad and Gharib found that the sensitivity and specificity of hepcidin $\leq$ 0.94 nmol/mmol for predicting ID was 88% [25]. Hepcidin appears to be a better predictor of iron availability during erythropoiesis than ferritin.

There is no agreement on how to characterize ID in preterm infants. Although bone marrow iron staining is thought to be the gold standard for identifying iron depletion [31], parents do not accept it due to its invasiveness. Ferritin is being used extensively to evaluate the iron status of preterm

infants; however, it cannot be used alone to detect iron insufficiency because it fluctuates over time and rises during infection and inflammation [32]. According to our regression study, ferritin is the strongest predictor of hepcidin, implying that hepcidin is related to iron storage, but not with circulating iron. This is consistent with the results of previous studies [33]. Hepcidin is usually inhibited to allow maximum absorption of iron in ID. Preterm infants are born with significantly lower hepcidin than full-term infants due to the small gestational age at birth and insufficient iron stores [20,34,35]. Serum hepcidin levels in preterm infants increase with gestational age, suggesting increased fetal acquisition of stored iron from the mother during late pregnancy. In preterm infants, hepcidin levels may reflect iron storage status.

One limitation of our study is the small sample size, which is attributable to the low incidence of preterm infants and the difficulties of blood collection, making it difficult to get blood samples for investigation. Another limitation of our study was the absence of a hepcidin reference range in preterm newborns. The minimum, 25%, 50%, 75% and maximum values of hepcidin at 6 months of corrected gestational age in preterm infants in this study were 0.78, 17.89, 27, 46.41 and 137.17 ng/ml, respectively. According to previous studies, the normal range of serum hepcidin concentration in adults is 0.6–23 ng/ml [36,37]. Mupfudze et al found median values of hepcidin in full-term infants at 3, 6 and 12 months to be 9.7 (2.5–19.25), 4.5 (0.49–7.32) and 1.9 (0.73–6.17) ng/ml, respectively [37]. Healthy Spanish infants had a mean hepcidin of 44.77 ± 1.5 and 54.28 ± 1.5 ng/ml at 6 and 12 months, respectively [27]. The preterm, term and adult hepcidin concentrations vary dramatically, and hepcidins are influenced by birth weight, gestational age, age, sex, inflammation, hypoxia and iron status. We need a large-scale clinical study to establish the reference range of hepcidin to guide the clinical management of ID and IDA in preterm infants.

5. Conclusion

The data from this study suggest that hepcidin may be a valid indicator of iron stores and a promising indicator for early diagnosis of ID in preterm infants. However, we need to conduct a large-scale clinical study to determine the reference range of hepcidin in preterm infants to guide the clinical management of ID in preterm infants.

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Conflict of interest

The authors declare no conflict of interest.

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