The Relation between Serum Hepcidin, Ferritin, Hepcidin: Ferritin Ratio, Hydroxyurea and Splenectomy in Children with β-Thalassemia

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Abstract

BACKGROUND: Hepcidin, a small peptide hormone, is established as the main regulator of iron homeostasis.

AIM: To estimate serum hepcidin, ferritin, and hepcidin: ferritin ratio in β-thalassemia patients and to determine the effect of splenectomy and hydroxyurea on serum hepcidin.

METHODS: A study was conducted on 30 thalassemia major (βTM), 29 thalassemia intermedia (βTI) and 29 healthy children’s controls. Data were collected by patient interviewing where detailed history-taking and thorough clinical examinations were carried out. Serum ferritin and hepcidin were measured by ELISA assay (Bioneovan Co. Ltd Beijing, China).

RESULTS: Beta-thalassemia patients had higher serum ferritin, serum hepcidin and lower Hb and hepcidin: ferritin ratio compared to the controls (p < 0.001, 0.010, 0.001, 0.001 respectively). B-TM patients had higher mean serum hepcidin and serum ferritin compared to β-TI, with statistically significant difference (P = 0.042, P < 0.001, respectively). Twenty-one patients out of 29 βTI was on hydroxyurea therapy; these patients had significantly lower levels of serum ferritin (P < 0.004) and significantly higher levels of Hb (P < 0.004). Serum ferritin was statistically significantly higher in spleenectomized patients P < 0.009. Serum hepcidin level was insignificantly higher in spleenectomized patients than non-spleenectomized patients (21.6 ± 14.75, 17.76 ± 10.01 ng/mL). Hepcidin showed a significantly positive correlation with hepcidin: ferritin ratio in all studied groups.

CONCLUSION: Serum hepcidin was elevated in β-thalassemia children with more evident elevation in BTM patients. Splenectomy played no major role in hepcidin regulation. Knowing that hepcidin in serum has a dynamic and multi-factorial regulation, individual evaluation of serum hepcidin and follow up, e.g. every 6 months could be valuable, and future therapeutic hepcidin agonists could be helpful in management of iron burden in such patient.

Introduction

Thalassemia remains a major haematological health problem in Egypt. B-thalassemia is autosomal recessive anaemia resulting from impaired biosynthesis of the β-globin chain [1]. This disorder of β-chain synthesis leads to ineffective erythropoiesis. Erythroid progenitor cells undergo intramedullary apoptosis and do not develop into mature erythrocytes. The basic mechanism of iron overload in children with β-thalassemia intermedia (TI) is the acceleration of the production of RBCs due to ineffective erythropoiesis [2], [3]. In children with β-thalassemia major (βTM) an adequate blood transfusion program decreases the complications of anaemia and compensatory bone marrow expansion, allows normal development throughout childhood, and extends survival [4]. Iron overload due to both transfused iron and increased iron absorption is common in BTM.

Significant progress was developed in clarifying the iron metabolism pathway. Hepcidin a small peptide hormone is established as main regulator of iron homeostasis. It inhibits iron entry into the plasma from the main sources of iron: dietary absorption, the release of stored iron from hepatocytes and the release of recycled iron from macrophages. However, in transfused patients higher hepcidin levels resulted in macrophage iron loading, whereas in nontransfused thalassemia, iron was deposited in hepatocytes [5]. Hepcidin is synthesized
as prohepcidin that is converted to its bioactive form by hepatocytes, secreted into the bloodstream, and excreted by the kidneys [5].

Furthermore, hepcidin is also synthesised in the spleen of normal mice and induced by lipopolysaccharide [6]. Camberlein et al. reported that hepcidin has led to restriction of iron export from the spleen, in a mouse model of secondary iron overload [7]. However, many authors reported that hepcidin is also produced from various tissues and organs, including adipose tissue, macrophages, monocytes and kidney, but at a lower level than that produced by the liver and the role of hepcidin in these cell types is unclear [8], [9], [10], [11]. Thalassemia is a good model to show the dynamic regulation of hepcidin in the face of competing influences of coexistent anaemia, expanded erythropoiesis and iron loading. Hepcidin level is variable in children with β-thalassemia [12], [13]. Cases with marked anaemia and high erythropoietic activity had hepcidin deficiency [14], but in case of iron overload, hepcidin expression will be increased [15]. In β-thalassemia, usually we depend on serum ferritin measurements to diagnose iron overload [16]. Knowing that, erythropoiesis measurably fluctuates over the inter transfusion interval, thus we must standardized the timing of measurement of indices for the research purposes (e.g. immediately pre-transfusion) [12].

Spleen is the most commonly affected organ in children with thalassemia. Splenomegaly is the result of extramedullary hematopoiesis, excessive destruction of abnormal RBCs, and transfusion overload. Splenomegaly further increases transfusion requirement. Splenic macrophages remove damaged RBCs passing through the red pulp of the spleen. Splenectomy is one possible therapeutic approach to the management of severely affected patients. Splenectomy is indicated when hypersplenism increases blood transfusion requirement and prevents adequate control of body iron with chelating therapy [17].

This study was conducted to estimate serum hepcidin, ferritin and hepcidin: ferritin ratio in β-thalassemia patients treated with hydroxyurea and different chelating therapy. Also, we aimed to determine the effect of splenectomy on serum hepcidin.

### Patients and Methods

The current case-control study was conducted in Pediatrics Clinic in the Centre of Excellence in National Research Centre and El Helal Giza Children Hospital haematology Clinic in 2018. The study included 59 patients, 30 TM and 29 TI. Patients consisted of 35 (59.3%) boys and 24 (40.7%) girls. Their age ranged from 3 – 17 y (mean age was 9.1 ± 3.7 y) and were diagnosed as β-TM and β-TI based on conventional clinical and hematologic criteria [18]. The exclusion criteria were ethose with concurrent infection, chronic inflammatory disorders or liver dysfunction. Also, 29 healthy subjects with matching age and sex were included as a control group. All patients and healthy subjects gave informed consent form to participate in the present study, approved by National Research Centre Ethics Committee. Data were collected by reviewing medical records as well as patient interviewing where detailed history-taking and thorough clinical examinations were carried out. Blood was collected before blood transfusion.

### Sample Collection

Four ml of venous blood were withdrawn under aseptic conditions; blood was centrifuged to get serum to measure liver function and kidney function tests. Serum samples then were stored in -80°C for assessment of serum ferritin and hepcidin.

### Laboratory Investigation

Liver function and kidney function tests were done by using an autoanalysier Olympus AU400 (Olympus America Inc, Center Valley, Pa, USA). Serum ferritin and hepcidin were measured by ELISA assay (Bioneovan Co. Ltd Beijing, China)

### Statistical analysis

The standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 17.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). The intergroup comparisons were performed by using an independent-sample t-test and a one-way analysis of variance and Chi-Square tests for categorical variables. Pearson’s and Spearman’s correlation tests (r=correlation coefficient) were used for correlating normal and nonparametric variables, respectively. Linear multiple regression was run to predict Hepcidin. Receiver operating curve (ROC) analysis was done to test the validity of hepcidin vs hepcidin to ferritin ratio in detecting iron overload. For all tests, a P-value of less than 0.05 was considered significant.

### Results

The mean age of the children with TM, TI and control were 10.3 ± 4.2 years (from 4 to 17 years), 9.1 ± 3.7 years (from 3 to 16 years) and 10.4 ± 4.2 years (from 2 to 18 years old) respectively, and there was...
no statistically significant difference between the three groups (P = 0.43) by ANOVA. Considering gender distributions, 21 (43.8%) and 22 (55%).

Of the subjects in the TM and TI groups were female, respectively; Considering gender distributions, patients consisted of 35 (59.3%) boys and 24 (40.7%) girls, there was no statistically significant difference (P = 0.39). Also, there were no statistically significant differences in serum hepcidin between males and females in patients with TM and TI (P = 0.56 respectively). Table 1 shows the comparison of Clinical and Laboratory Data of β-thalassemia Patients with controls. β-thalassemia patients had higher serum ferritin, serum hepcidin, lower Hb and hepcidin: ferritin ratio compared to the control group (p < 0.001, 0.010, 0.001, 0.001, respectively).

Table 1: Comparison of Clinical and Laboratory Data of β-thalassemia Patients With controls

|                | N | Mean  | Std. Deviation | Sig. (2-tailed) |
|----------------|---|-------|----------------|----------------|
| Age (Years)    |   |       |                |                |
| β-thalasemia   | 59| 9.18  | 3.70           | 0.193          |
| Controls       | 29| 10.34 | 4.24           |                |
| Hb (g/dL)      |   |       |                |                |
| β-thalasemia   | 59| 7.24  | 1.03           | 0.001          |
| Controls       | 29| 11.68 | 1.08           |                |
| Ferritin (ng/mL) | 59| 1581.6 | 787.64        | 0.001          |
| Patients       | 29| 141.9 | 55.33          |                |
| Hepcidin (ng/mL) | 59| 19.73 | 12.98          | 0.010          |
| Patients       | 29| 13.01 | 6.46           |                |
| Hepcidin/ferritin Ratio | 59| 0.023 | 0.043         | 0.001          |
| Controls       | 29| 0.094 | 0.0365         |                |

When the two groups of thalassemia (TM, TI) were considered separately, age and hepcidin: ferritin ratio showed no statistically significant difference between the two groups. On the other hand, β-TM patients had higher mean serum hepcidin, serum ferritin, lower Hb and lower number of weeks between transfusions compared to β-TI, with statistically significant difference (P=0.042, P < 0.001 respectively) (Table 2).

Table 2: Comparison of Clinical and Laboratory Data of Patients With β-Thalassemia Major and Intermedia

|                | N | Mean  | Std. Deviation | Sig. (2-tailed) |
|----------------|---|-------|----------------|----------------|
| Age (Years)    |   |       |                |                |
| βm             | 30| 9.23  | 3.80           | 0.022          |
| Bti            | 30| 9.13  | 3.47           |                |
| BMI            |   |       |                |                |
| Bm            | 30| 16.93 | 3.58           | 0.791          |
| Bti           | 30| 17.16 | 3.02           |                |
| No of weeks between blood transfusion |   |       |                |                |
| Bm            | 30| 3.80  | 0.407          | 0.001          |
| Bti           | 29| 8.66  | 5.79           |                |
| Hb (g/L)      |   |       |                |                |
| Bm            | 30| 6.59  | 0.94           | 0.001          |
| Bti           | 29| 7.91  | 0.59           |                |
| Ferritin (ng/mL) | 30| 2039.10 | 574.50       | 0.001          |
| Bm            | 29| 1046.37 | 599.67       |                |
| Bti           | 29| 21.74 | 13.11          | 0.042          |
| Hepcidin (ng/mL) | 30| 16.04 | 9.31           | 0.135          |
| Bm            | 30| 0.026 | 0.057          | 0.598          |
| Bti           | 29| 0.020 | 0.01           |                |

Table 3 shows iron chelation therapy (deferoxamine = DFO; deferiprone = DFP and deferasirox = DFX) in patients with β-thalassemia major and intermedia. There was a statistically significant difference between the two groups regarding the type of chelating agents and the number of patients (P < 0.001). Out of 59 patients 17 patients with β-thalassemia intermedia did take iron chelation therapy. None chelated group had significantly lower levels of serum ferritin (787.00 ± 272.04 and 1903.31 ± 693.48 P < 0.001). Also, they had a significantly higher mean Hb level (8.16 ± 0.499 and 6.87 ± 0.95 P < 0.001).

Twenty-one patients out of 29 βTI were on hydroxyurea therapy, these patients had significantly lower levels of serum ferritin (P < 0.004) and significantly higher levels of Hb (P < 0.004) than other patients. The insignificant difference was found in serum hepcidin and hepcidin:ferritin ratio between the two groups.

Transfusion dependent TI patients had significantly higher serum ferritin (P < 0.001) and significantly lower Hb (P < 0.007). Serum hepcidin and hepcidin: ferritin ratio showed no statistically significant difference between the dependent and non-dependent groups.

The relationship between iron overload and laboratory data among thalassemia patients are shown in Table 4. There was a statistically significant difference in number of weeks between blood transfusion, Hb g/L, ferritin ng/mL, hepcidin ng/mL and hepcidin: ferritin ratio (P < 0.005, 0.001, 0.001, 0.007 and 0.001) respectively.

Table 3: Types of Chelating Agents in Patients With β-Thalassemia Major and Intermedia

| Type of chelation | Total |
|-------------------|-------|
|                  |       |
| β-TM              |       |
| % within Thalassemia Major Thalassemia | 0.0% |
| Controls          | 100.0% |
| % within Type of chelation |       |
| Count             | 17    |
| % within Thalassemia Intermedia |       |
| Controls          | 62.0% |
| % within Type of chelation |       |
| Count             | 17    |
| % within Thalassemia Major Thalassemia | 60.0% |
| Controls          | 58.6% |
| % within Type of chelation |       |
| Count             | 17    |
| % within Thalassemia Intermedia | 40.0% |
| Controls          | 28.6% |
| % within Type of chelation |       |
| Count             | 17    |

Table 4: Comparison of Clinical and Laboratory Data of Patients with Iron Overload and Without

| Iron overload | No iron overload | N | Mean  | Std. Deviation | Sig. (2-tailed) |
|---------------|------------------|---|-------|----------------|----------------|
| (SF ≥ 1000 ng/ml) |                  |   |       |                |                |
| Age (Years)   | No iron overload | 49| 9.69  | 3.92           | 0.737          |
| Bm            | Iron overload    | 39| 9.41  | 3.92           |                |
| BMI           | No iron overload | 20| 16.78 | 3.31           | 0.671          |
| Bm            | Iron overload    | 39| 17.17 | 3.31           |                |
| Ferroin (ng/mL) | No iron overload | 20| 8.65  | 5.84           | 0.005          |
| Bm            | Iron overload    | 39| 5.08  | 3.64           |                |
| Hepcidin (ng/mL) | No iron overload | 49| 10.17 | 2.04           | 0.001          |
| Bm            | Iron overload    | 39| 6.86  | 1.01           |                |
| Hepcidin:Ferritin Ratio | No iron overload | 49| 369.70 | 292.53       | 0.001          |
| Bm            | Iron overload    | 39| 2033.80 | 564.25      |                |
| Hepcidin (ng/mL) | No iron overload | 49| 14.55 | 8.68           | 0.007          |
| Bm            | Iron overload    | 39| 21.25 | 13.39          |                |
| Hepcidin:Ferritin Ratio | No iron overload | 49| 0.066 | 0.046         | 0.001          |
| Bm            | Iron overload    | 39| 0.023 | 0.051         |                |

Considering splenectomy, 18 cases out of 59 (30.5%) had a splenectomy. Although serum hepcidin level was higher in splenectomized patients (21.6 ± 14.75, 17.76 ± 10.01 ng/mL), there was no statistically
significant difference in number of weeks between blood transfusion, Hb g/L, hepcidin ng/mL and hepcidin: ferritin ratio between splenectomized patients and non-splenectomized. Serum ferritin ng/mL was statistically significantly higher in splenectomized patients P < 0.009. Also, 15 out of 18 splenectomized patients had iron overload (serum ferritin ≥ 1000 ng/ml) as shown in Table 5.

Table 5: Results of splenectomized and non-splenectomized TM patients

| Group               | Splenomegaly | N  | Mean   | Std. Deviation | Sig. (2-tailed) |
|---------------------|--------------|----|--------|----------------|-----------------|
| Hpd levels          |              |    |        |                |                 |
| Hpd                  | 1            | 20 | 19.7605| 11.09305       | 0.245           |
| Hpd                  | 1            | 10 | 25.7400| 16.37024       |                 |
| Ferritin            | 1            | 20 | 0.01952| 0.0254222      | 0.344           |
| Ferritin            | 1            | 10 | 0.04102| 0.0947943      |                 |
| Hpd                  | 1            | 20 | 2103.6250| 676.39623 | 0.953           |
| Hpd                  | 0            | 10 | 2050.0650| 312.33822 |                 |
| Hpd                  | 0            | 10 | 6.6750| 0.91931        | 0.514           |

Hepcidin showed a significantly positive correlation with Hepcidin: ferritin ratio in all studied groups. Also, it showed a significantly negative correlation with age in patients with β-thalassemia. Healthy children hepcidin showed a significantly positive correlation with ferritin (r = 0.645, P < 0.001), as shown in Table 6.

Table 6: Results of correlation between serum hepcidin levels and the evaluated parameters for all groups

| Group        | Age (years) | Ferritin (ng/mL) | Hemoglobin (g/L) | Hpd/ferritin ratio (g/mL) | P-value |
|--------------|-------------|------------------|------------------|---------------------------|---------|
| β-thalasemia |              |                  |                  |                           |         |
| β-TM         | -0.317**    | -0.014           | 0.617            | 0.012                     | 0.751** |
| β-TI         | -0.342**    | -0.058           | 0.760            | 0.082                     | 0.747** |
| Controls     | 0.300**     | 0.114            | 0.645**          | 0.001                     | 0.583** |

Multiple linear regression was run to predict hepcidin from Predictors: (Constant), hydroxyurea therapy, hepcidin/ ferritin, transfusion, hepcidin, and ferritin in diseased children. Serum ferritin and hepcidin: ferritin ratio variables were a statistically significant predictor of serum hepcidin level (P < 0.001).

A receiver operating characteristic curve (ROC curve) was done to test the sensitivity and specificity of hepcidin and hepcidin/ferritin ratio, in predicting iron overload (SF ≥ 1000 ng/ml) at different cutoff values. The area under the curve of hepcidin was found as 0.628 (P = 0.040) while that of hepcidin/ferritin ratio was 0.180 (non-sig), indicating that overall predictability of hepcidin is significantly high when compared to hepcidin/ferritin ratio (Figure 1).

Discussion

Hepcidin level in serum has a dynamic and multifactorial regulation. The current study showed that β-thalassemia patients of both βTM and βTI had significantly elevated serum hepcidin level compared to healthy children. Our results were in agreement with those of previous studies [19], [20], [21]. On other hand, several authors reported undetectable or low serum hepcidin in β-TM subjects as compared to controls [22], [23], [24], [25], [26]. Hepcidin has a complex regulation in β-thalassemia patients. Its production is controlled by opposing effects from erythropoiesis, anaemia and iron overload. Hepcidin is up-regulated by increased body iron levels, infection and inflammation; it is down-regulated by many factors as anaemia, hypoxia, iron deficiency, ineffective erythropoiesis and by increased levels of erythropoietin [13], [27], [28], [29]. It may be valuable to know that other factors might modify the hepcidin synthesis in β-thalassemia patients such as genetic or laboratory variables [27], [30]. Our data showed that patients with βTM had significantly higher serum hepcidin than βTI cases. The rate of iron loading is higher in βTM than in βTI due to regular transfusions also transfusions inhibit erythropoietic drive; both lead to an increase of hepcidin in β-TM patients [14], [19], [21], [23], [24].

Our data showed that serum hepcidin is not affected by gender in children with β-thalassemia this was in agreement with previous studies [21], [22], [23], [24].

The current study showed no significant difference in serum hepcidin between TI patients receiving hydroxyurea and those not receiving hydroxyurea, although they had significantly higher levels of Hb (P < .004). This means that hydroxyurea intake did not affect hepcidin production directly or through increasing total haemoglobin level. Or probably Hb was not high enough to suppress ineffective erythropoiesis and consequently, was not able to decrease serum hepcidin level. Our result was in agreement with Haghpanah et al., [21], [29].

Considering splenectomy, eighteen (30.5%) of our patients had been splenectomized. Although
serum hepcidin level was higher in splenectomized patients, the difference was of no statistical significance. Jones et al., reported that the inflammatory marker CRP and transferrin saturation both were higher in splenectomized patients. Both inflammation and transferrin bound iron is known to induce hepcidin [1]. Splenectomy in Hb E β-thalassemia patients was associated with lower serum hepcidin; the authors reported that the differences in hepcidin were not mediated by a phenotype-splenectomy interaction [31]. Similar to a previous study, we found no difference in Hb between splenectomized and non-splenectomized patients [1], [32]. There was no apparent difference in hepcidin: ferritin ratio between splenectomized patients and non-splenectomized patients.

The authors found that age has no relation with hepcidin level among healthy children; this was in agreement with previous report [21], [29]. But in children with βTM, negative correlation between age and hepcidin was reported. Based on the current study results, there was insignificant correlation between serum hepcidin and ferritin levels in patients with βTM and βTI, which supported the results of previous studies that regulation of serum hepcidin in thalassemia is more affected by erythropoietic activity than by iron, overload [29], [33].

The hepcidin/ferritin ratio in β-thalassemia children was significantly lower (P < 0.0001) than in controls suggesting that serum hepcidin level was not increased in proportion to the iron overload [13], [29]. Hepcidin showed a significantly positive correlation with hepcidin: ferritin ratio in all studied groups.

Using a receiver operating characteristic curve (ROC curve) in predicting iron overload, it was found that area under the curve (AUC) of hepcidin was 0.628; which indicates that the overall predictability of hepcidin is significant (p = 0.040). Accuracy is measured by the area under the ROC curve. An area of 0.60-0.70 represents a poor test; this result was similar to a previous study [21]. The result means that serum hepcidin was not as good as serum ferritin in predicting severe iron overload.

There were some limitations in the study since we did not evaluate molecular erythropoietic activity. The liver iron concentration was not available for the present cases to be the gold standard of assessment of iron overload.

In conclusion, based on the current study results, serum hepcidin was elevated in β-thalassemia children with more evident elevation in βTM patients. Also serum hepcidin levels were significantly higher in the βTM than in βTI patients, which could be due to higher erythropoietic activity in TI. Splenectomy played no major role in hepcidin regulation. There was insignificant correlation between serum hepcidin level and serum ferritin level as a marker of iron overload in patients with βTM and βTI. Knowing that hepcidin in serum has a dynamic and multi-factorial regulation, individual evaluation and follow up, e.g. every 6 months could be valuable in diagnosing and managing iron burden in such patient. Future therapeutic hepcidin agonists could be helpful in management of iron burden in β thalassemia.

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