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## The role of urinary hepcidin in early detection of iron deficiency anemia

Aisha El Sheimy

*National Institute of Urology and Nephrology*

Azza Omran

*El-Mataria Teaching Hospital*

Fify Helmy

*El-Mataria Teaching Hospital*

Hala I. Mouhamed

*National Institute of Urology and Nephrology, rama\_rama\_1997@hotmail.com*

Sohaila Ali

*El-Mataria Teaching Hospital*

*See next page for additional authors*

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### Authors

Aisha El Sheimy, Azza Omran, Fify Helmy, Hala I. Mouhamed, Sohaila Ali, and Youssof Mohamed

# The role of urinary hepcidin in early detection of iron deficiency anemia

Hala I. Mouhamed<sup>a</sup>, Aisha El Sheimy<sup>a</sup>, Azza Omran<sup>b</sup>, Youssef Mohamed<sup>b</sup>, Fify Helmy<sup>b</sup>, Sohaila Ali<sup>b</sup>

<sup>a</sup>National Institute of Urology and Nephrology, <sup>b</sup>El-Mataria Teaching Hospital, Cairo, Egypt

## Abstract

Iron deficiency anemia (IDA) is one of the most severe and important nutritional deficiencies, especially in children all over the world. Iron deficiency may occur because of inadequate dietary intake, increase in physiological needs of the nutrient, and/or increased losses, which may lead to anemia. IDA has been associated with cognitive, motor, and behavioral impairment in children. The most commonly used tests to determine iron status include serum iron levels, ferritin, and others. However, these test have limited role in diagnosis of IDA. For this reason, there is great interest in investigating effective method for the diagnosis of IDA. The use of urinary hepcidin as a biomarker for the regulation of iron metabolism and its level decreased with IDA.

**Keywords:** Anaemia, detection, urinary hepcidin

## INTRODUCTION

Iron is an essential element for nearly all living organisms. Iron is a key component of oxygen storage and transporting proteins, such as hemoglobin (Hb) and myoglobin, and of many enzymes that catalyze oxidation-reduction reaction necessary to generate energy and produce various metabolic intermediates for host defense [1]. The concentration of iron in biological fluids is tightly regulated to provide iron as needed and decreased iron levels can lead to anemia [2]. Thus, maintenance of body iron stores is essential, because many human diets contain iron sufficient only to replace the small iron losses [3]. Iron deficiency may occur because of inadequate dietary intake, increase in physiological needs of the nutrient, and/or increased losses, which may lead to anemia [4]. Iron deficiency anemia (IDA) is one of the most severe and important nutritional deficiencies in the world [5]. IDA has been associated with cognitive, motor, and behavioral impairment in children. IDA is also one of the most common causes of anemia, especially in women of child-bearing age and children under 2 years of age [6]. The most commonly used tests to determine iron status include serum iron levels and ferritin, which is used as an indicator of iron stores; soluble transferrin receptors levels, which reflect tissue iron stores and transferrin saturation level. However, these test

have limitation such that ferritin level may be elevated in patients with co-existing inflammation, soluble transferrin receptor levels may be influenced by erythropoietic activity, and transferrin saturation may be affected by inflammation and diurnal variation [7].

For this reason, there is great interest in investigating effective method for the diagnosis of IDA. The use of hepcidin as a biomarker for the regulation of iron metabolism was investigated by Hoppe *et al.* [8]. Hepcidin has evolved as the primary regulator of iron homeostasis and a probable mediator of anemia of chronic disease and inflammation [9]. Hepcidin, is the principle iron-regulatory hormone that mediates the homeostasis of extracellular iron concentration. Hepcidin is initially synthesized as an 84-amino acid preprohepcidin, then it is processed in hepatocyte by a signal peptidase and the prohormone convertase furin to its bioactive form, 25-amino acid peptide [10]. Hepcidin is produced by hepatocytes and is rapidly cleared from the circulation [11]. It is the key hormone that regulates systemic iron homeostasis. It inhibits the transport of iron across the gut mucosa, thereby preventing

**Correspondence to:** Hala I. Mohamed, MD,  
Laboratory Department, National Institute of Urology and Nephrology,  
El-Mataria Teaching Hospital, Cairo, Egypt.  
Tel: 01002015859.  
E-mail: rama\_rama\_1997@hotmail.com

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excess iron absorption and maintaining iron levels within normal limits in the body. It also inhibits transport of iron out of macrophage [12].

Three hepcidin isoforms (hepcidin-20, hepcidin-22, and hepcidin-25) are excreted in urine. Hepcidin-25 and hepcidin-20 are also found in the serum [13]. Hepcidin-25 is the only isoform that has a dominant role in iron regulation [14]. Estimation of hepcidin levels for diagnosis and prognosis of anemia may provide a more effective approach for the treatment of IDA and prevention of toxicity associated with the iron overload [15].

### Aim

Early detection of anemia in children by detecting urinary hepcidin level to begin an early treatment before overt IDA and avoid complications.

## PATIENTS AND METHODS

This study was performed on 90 children, 70 children with different stages of IDA, their ages ranged between 4 and 6 years (32 males and 38 females), and 20 healthy children as a control group with matched age and sex. All were recruited from outpatient clinic at El-Mataria Teaching Hospital from December 2015 to January 2017. According to the iron deficiency state, the patients were divided into three groups:

Group I: 25 children with normal iron and hematological parameters [Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC)] except low serum ferritin level (stage I iron deficiency)

Group II: 23 children presented with low serum iron, ferritin, and % saturation (stage II IDA).

Group III: 22 children with low serum iron, all hematological parameters, ferritin, and % saturation (stage III IDA).

Control group: 20 healthy children with normal hematological and iron parameters.

Patients who had inflammation, infection, liver, and kidney diseases. Also patients on iron therapy in the previous 3 months were excluded from this study.

Patients and control children enrolled in this study were subjected to full history taking and complete clinical examination. Laboratory investigations that included the following: complete blood count (Sysmex XS 500i, Norderstedt, Germany), liver, kidney functions using (automated chemistry system Vitros 350, Raritan, NJ), serum iron, Total iron-binding capacity (TIBC), and % saturation were performed by Centronic GmbH Kit (Am Klein Feld11, Wartenberg, Germany) using spectrophotometer, Berlin, Germany (5010). Serum ferritin assay using quantitative test was based on a solid phase enzyme-linked immunoassay (Biocheck Inc., Foster City, California, USA), and random urinary sample for hepcidin assay. Midstream clean catch urine sample was

collected and placed on ice until centrifuged at 2000g for 6 min. The supernatant was stored at  $-80^{\circ}\text{C}$  for subsequent analysis. Measurement of hepcidin-25 in urine, which is the biologically active form of the hormone, using solid phase competitive enzyme-linked immunosorbent assay kit (Backman S-1337 EIA, South Kraemer Boulevard Brea, California).

### Statistical analysis

Recorded data were analyzed using the statistical package for the social sciences (version 20.0; SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean  $\pm$  SD. Qualitative data were expressed as frequency and percentage. A one-way analysis of variance when comparing between more than two means.  $\chi^2$  test of significance was used to compare proportions between two qualitative parameters. Pearson's correlation coefficient ( $r$ ) test was used for correlating data. Receiver operating characteristic (ROC) curve analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value. So, the  $P$  value was considered significant as the following:

- (1)  $P$  value less than 0.05 was considered significant.
- (2)  $P$  value less than 0.001 was considered as highly significant.
- (3)  $P$  value more than 0.05 was considered insignificant.

## RESULTS

Positive significant correlation between urinary hepcidin and all parameters, also significant negative correlation between TIBC and urinary hepcidin, whereas age was nonsignificant (Figs 1–10 and Tables 1–5).

ROC curve was used to define the best cut-off value of urinary hepcidin in group I, group II, and group III ( $<0.95$ ,  $<0.38$ , and  $<0.089$ ), respectively.

## DISCUSSION

IDA is one of the most common nutritional disorders in children all over the world. The most important key mediator of anemia is a peptide hepcidin. It is a regulator of systemic iron metabolism, and can help in diagnosis of IDA among children even before routine hematological parameters and iron profile diagnosis anemia. It is a conserved 25-amino acid peptide produced in the liver and detectable in blood and urine. It is induced by iron stores and inflammation, and function as a signal inhibiting iron absorption in small intestine and sequestering iron in macrophage [16]. Hepcidin is regulated by iron concentrations in plasma and by erythropoietic demand for iron in a feedback manner [17]. Although measurements of urinary hepcidin and serum ferritin correlate in patients with different iron disorders, and both are shown to be regulated by iron and inflammation [18]. Hepcidin is thus a type II acute phase reactant protein that provides a link between inflammation, resulting anemia, and the regulation of iron metabolism. Ferritin is an indicator of storage iron, but its level are elevated in patients with coexisting inflammation. Similarly transferrin saturation

**Table 1: Comparison between groups according to all parameters, using one-way analysis of variance test**

|                            | Control group | Group I (stage I anemia) | Group II (stage II anemia) | Group III (stage III anemia) | ANOVA    | P      |
|----------------------------|---------------|--------------------------|----------------------------|------------------------------|----------|--------|
| Age (years)                |               |                          |                            |                              |          |        |
| Mean±SD                    | 4.98±0.83     | 5.04±0.82                | 5.20±0.69                  | 4.52±0.66                    | 2.294    | 0.054  |
| Range                      | 4-6           | 4-6                      | 4-6                        | 4-6                          |          |        |
| Sex [n (%)]                |               |                          |                            |                              |          |        |
| Female                     | 12 (60)       | 13 (52)                  | 13 (56.5)                  | 12 (54.5)                    | 0.306    | 0.959  |
| Male                       | 8 (40)        | 12 (48)                  | 10 (43.5)                  | 10 (45.5)                    |          |        |
| Hb (g/dl)                  |               |                          |                            |                              |          |        |
| Mean±SD                    | 12.55±0.79    | 12.61±0.75               | 12.44±0.77                 | 8.05±0.66                    | 202.459  | <0.001 |
| Range                      | 11.3-14.2     | 11.6-14                  | 10.8-13.6                  | 6.9-9.2                      |          |        |
| HCT (%)                    |               |                          |                            |                              |          |        |
| Mean±SD                    | 36.12±2.07    | 39.57±9.47               | 36.73±1.87                 | 22.75±1.56                   | 46.351   | <0.001 |
| Range                      | 33.9-40       | 34.8-84.1                | 33.9-39.9                  | 20.4-25.8                    |          |        |
| MCV (fl)                   |               |                          |                            |                              |          |        |
| Mean±SD                    | 86.88±4.45    | 86.79±4.56               | 84.54±4.01                 | 60.99±2.38                   | 223.701  | <0.001 |
| Range                      | 79.8-95.7     | 79.5-94.1                | 79.1-92.7                  | 57.1-64.6                    |          |        |
| MCH (pg)                   |               |                          |                            |                              |          |        |
| Mean±SD                    | 26.87±1.53    | 27.20±1.78               | 26.96±1.71                 | 21.83±1.41                   | 57.057   | <0.001 |
| Range                      | 24.2-29.5     | 23.8-30.2                | 24-30.2                    | 19.2-24.1                    |          |        |
| MCHC (g%)                  |               |                          |                            |                              |          |        |
| Mean±SD                    | 34.23±1.50    | 35.12±1.71               | 33.66±1.88                 | 25.28±1.89                   | 150.940  | <0.001 |
| Range                      | 31.2-36.8     | 31.9-37.4                | 30.8-37                    | 21.9-28.5                    |          |        |
| Fe (µg/dl)                 |               |                          |                            |                              |          |        |
| Mean±SD                    | 90.71±4.96    | 85.91±6.39               | 50.79±5.14                 | 20.44±1.07                   | 1001.572 | <0.001 |
| Range                      | 78.5-100.2    | 74.5-102.2               | 42.6-59.4                  | 19-22.6                      |          |        |
| Ferritin (ng/ml)           |               |                          |                            |                              |          |        |
| Mean±SD                    | 69.30±6.67    | 16.40±1.06               | 9.70±1.16                  | 5.15±0.69                    | 1729.747 | <0.001 |
| Range                      | 55.4-85.2     | 15.1-20                  | 7.9-11.9                   | 4-6.6                        |          |        |
| TIBC (µg/dl)               |               |                          |                            |                              |          |        |
| Mean±SD                    | 258.50±7.20   | 247.68±20.44             | 387.74±18.22               | 486.50±13.34                 | 1129.484 | <0.001 |
| Range                      | 250-275       | 215-287                  | 350-418                    | 460-506                      |          |        |
| Transferrin saturation (%) |               |                          |                            |                              |          |        |
| Mean±SD                    | 34.97±2.61    | 34.78±1.22               | 13.27±1.37                 | 4.17±0.30                    | 2233.16  | <0.001 |
| Range                      | 27.2-39       | 32.9-37.2                | 11.2-16.8                  | 3.7-4.9                      |          |        |

This table shows statistically significant difference between groups according to all parameters, whereas age and sex were nonsignificant. ANOVA, analysis of variance; Fe, iron; Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

**Table 2: Comparison between groups according to urinary hepcidin, using one-way analysis of variance test**

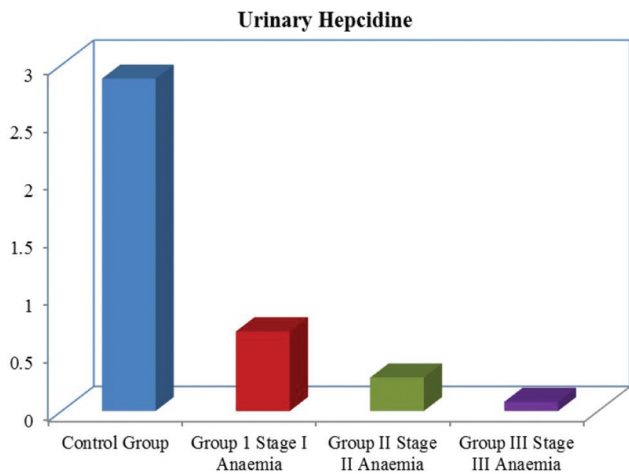
| Urinary hepcidin | Control group | Group I (stage I anemia) | Group II (stage II anemia) | Group III (stage III anemia) | ANOVA   | P      |
|------------------|---------------|--------------------------|----------------------------|------------------------------|---------|--------|
| Mean±SD          | 2.88±0.82     | 0.69±0.16                | 0.29±0.05                  | 0.08±0.00                    | 216.937 | <0.001 |
| Range            | 1.49-4.12     | 0.41-0.95                | 0.21-0.38                  | 0.072-0.089                  |         |        |

This table shows highly statistically significant difference between groups according to the urinary hepcidin. ANOVA, analysis of variance.

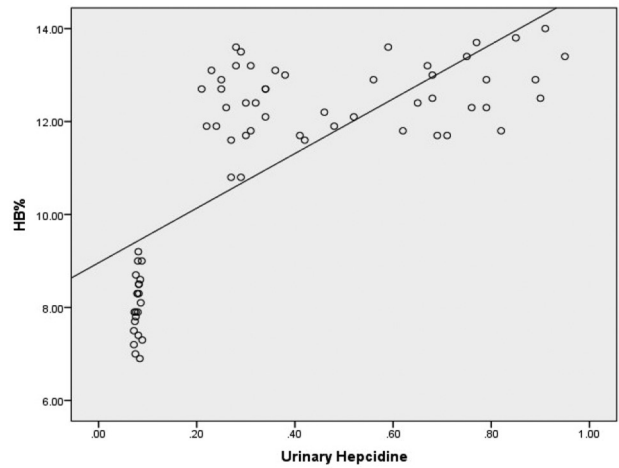
level may be affected by inflammation and undergoes diurnal variation [19]. The study revealed statistically significant decreased ( $P < 0.001$ ) Hb level, red cells indices including MCV, mean corpuscular hemoglobin, and MCHC in three groups compared with control group (Table 1), reflecting hypochromic and microcytic anemia type of IDA. Whereas, there was no statistical difference according to age and sex ( $P = 0.054$ ).

In our study, urinary hepcidin levels were significantly lower in all stages ( $0.69 \pm 0.16$ ,  $0.29 \pm 0.05$ ,  $0.08 \pm 0.00$ )

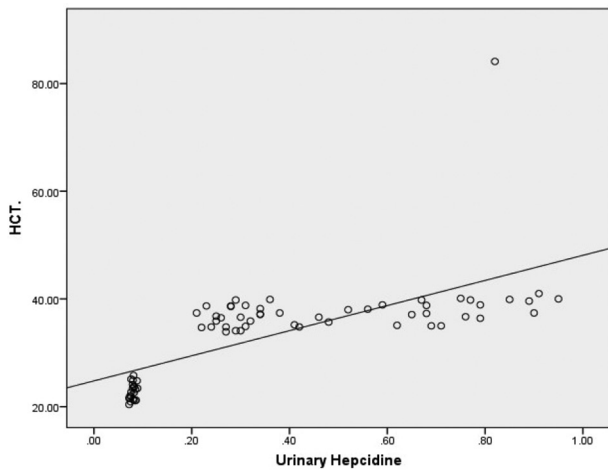
in group I, group II, and group III, respectively, than in control group ( $2.88 \pm 0.82$ ) ( $P < 0.001$ ) (Table 2). More significant reduction in its level was observed with the progress in the severity of anemia. This was in agreement with Cherian *et al.* [14] who found that urinary hepcidin were significantly lower in iron deficiency and IDA. Iron regulates hepcidin homeostatically, increased iron levels in plasma, and iron storage stimulates the production of hepcidin.



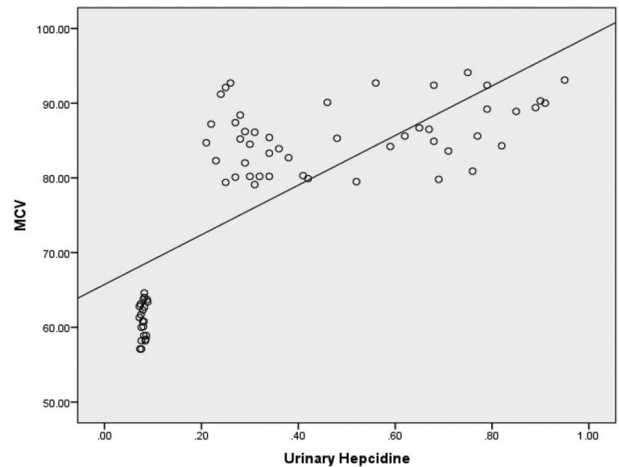
**Figure 1:** Bar chart between groups according to urinary hepcidin.



**Figure 2:** Scatter plot between urinary hepcidin and Hb (g/dl). Hb, hemoglobin.



**Figure 3:** Scatter plot between urinary hepcidin and HCT. HCT, hematocrit.



**Figure 4:** Scatter plot between urinary hepcidin and MCV. MCV, mean corpuscular volume.

**Table 3: Correlation between urinary hepcidin and all parameters, using Pearson's correlation coefficient in all patient group**

| Parameters                 | Urinary hepcidin |        |
|----------------------------|------------------|--------|
|                            | R                | P      |
| Age (years)                | 0.215            | 0.074  |
| Hb (g/dl)                  | 0.731            | <0.001 |
| HCT (%)                    | 0.690            | <0.001 |
| MCV (fl)                   | 0.751            | <0.001 |
| MCH (pg)                   | 0.653            | <0.001 |
| MCHC (g%)                  | 0.740            | <0.001 |
| Serum iron (µg/dl)         | 0.958            | <0.001 |
| Ferritin (ng/ml)           | 0.947            | <0.001 |
| TIBC (µg/dl)               | -0.893           | <0.001 |
| Transferrin saturation (%) | 0.939            | <0.001 |

Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Hepcidin production is also regulated by the erythropoietic process, whose core activity is characterized by iron

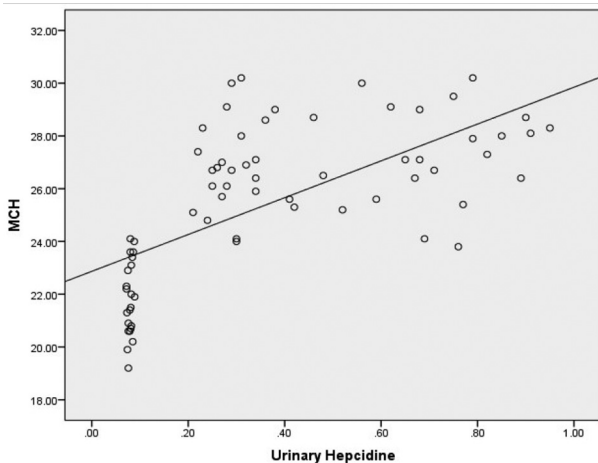
consumption. So, in anemia hepcidin suppression causes the stored iron to be released by hepatocytes and macrophages, whereas the intestinal absorption of iron increases [20]. The feedback loop between iron and hepcidin ensures stability of plasma iron concentration [15]. In our study ROC curve was used to define the best cut-off value of urinary hepcidin in group I, group II, and group III ( $\leq 0.95$ ,  $\leq 0.38$ ,  $\leq 0.089$ ), respectively, in healthy children. These three cut-off points had strong confidence intervals and valuable predictive potentials (Table 4).

Guyatt *et al.*, 1992 calculated the predictive value and area under the ROC curve for serum ferritin in detection of IDA. Area under the ROC was 0.95 compared to 0.77 for MCV, 0.74 for transferrin saturation, and 0.62 for absolute red cell distribution wideness ( $P < 0.001$ ) [21]. In our study, urinary hepcidin levels at cut-off point less than or equal to 0.95 nmol/mmol Creatinine (Cr) could predict ID stage I with sensitivity 100% and specificity 100%. Further, urinary hepcidin levels at cut-off point less than or equal to 0.38 nmol/

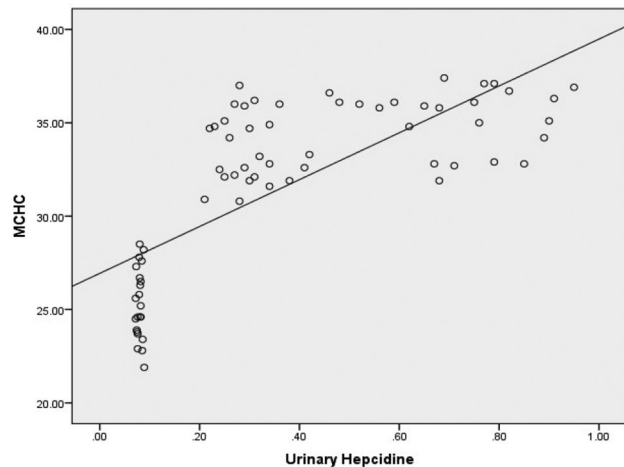
**Table 4: Diagnostic performance of urinary hepcidin in discrimination of control and other state**

| Groups              | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|---------------------|---------|-----------------|-----------------|---------|---------|--------------|
| Control vs. group I | <0.95   | 100             | 100             | 100     | 100     | 100          |
| Control vs. group I | <0.38   | 100             | 100             | 100     | 100     | 100          |
| Control vs. group I | <0.089  | 100             | 100             | 100     | 100     | 100          |

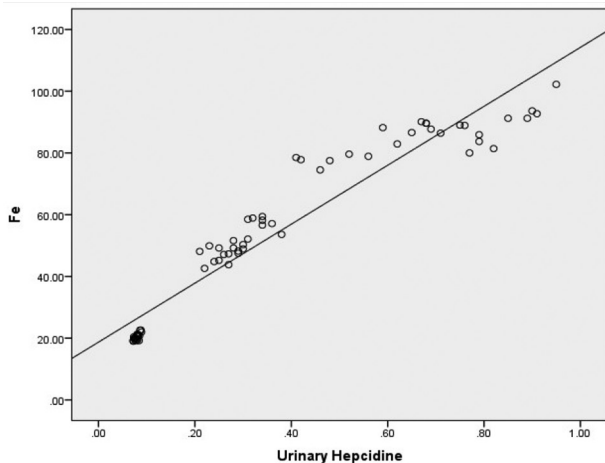
NPV, negative predicative value; PPV, positive predicative value.



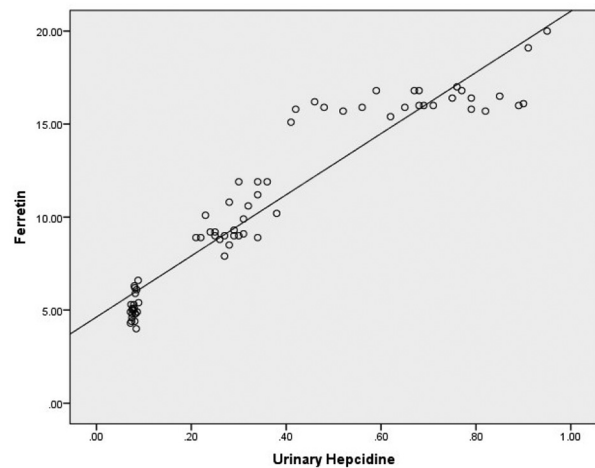
**Figure 5:** Scatter plot between urinary hepcidin and MCH. MCH, mean corpuscular hemoglobin.



**Figure 6:** Scatter plot between urinary hepcidin and MCHC. MCHC, mean corpuscular hemoglobin concentration.



**Figure 7:** Scatter plot between urinary hepcidin and Fe. Fe, iron.



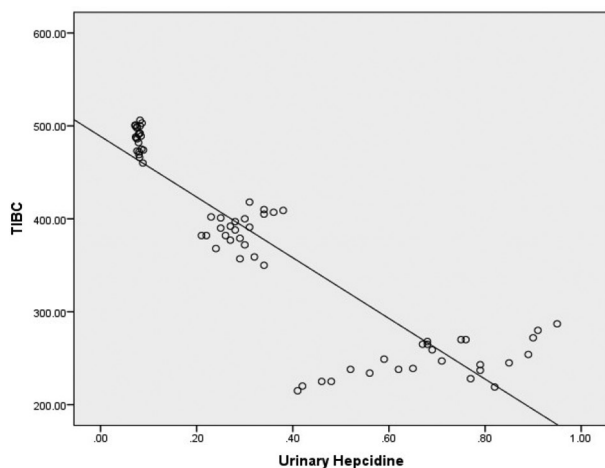
**Figure 8:** Scatter plot between urinary hepcidin and ferritin.

mmol Cr could predict ID stage II with sensitivity 100% and specificity 100%. Also, urinary hepcidin levels at cut-off point less than or equal to 0.089 nmol/mmol Cr could predict ID stage III with sensitivity 100% and specificity 100% (Table 4).

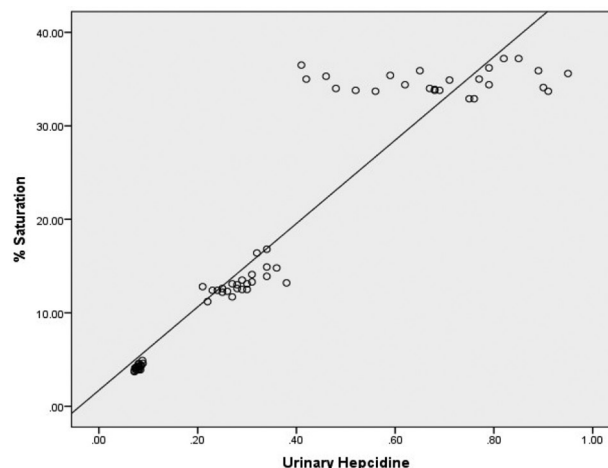
There is a shortage of iron available to the erythroid precursors in the bone marrow for Hb synthesis in the third stage of ID. Hb levels may be reduced but the resulting mild anemia may not be detectable using normal cut-off values for Hb. Iron-deficient erythropoiesis may be undetectable by using traditional laboratory parameters. In first and second stages of anemias, storage iron may be normal or even increased due to impaired release of iron into the circulation (Melis

*et al.*, 2008) [22]. Beutler *et al.* (2006) [23] stated that there is no overt effect on erythropoiesis in first stage of ID, blood Hb levels are usually normal, and ID generally can escape detection by Hb or hematocrit screening. The ferritin level increases with age, and it is acute phase reactant that may be elevated in the setting of chronic inflammation, malignancy, and chronic renal failure (Pak *et al.*, 2006) [24]. So, performing bone marrow aspiration may provide more explanation about this finding through estimation of stainable tissue iron.

Reduced urinary hepcidin is an essential part of the physiological response to an IDA. Decreased hepcidin and serum ferritin along with other indices signals that increased iron is needed.



**Figure 9:** Scatter plot between urinary hepcidin and TIBC.



**Figure 10:** Scatter plot between urinary hepcidin and % transferrin saturation.

**Table 5: Receiver operating characteristic curve diagnostic performance of urinary hepcidin in discrimination of control and other state**

|                            | Urinary hepcidin |        |
|----------------------------|------------------|--------|
|                            | R                | P      |
| <b>Group I</b>             |                  |        |
| Age (years)                | 0.045            | 0.832  |
| Hb (g/dl)                  | 0.530            | 0.006  |
| HCT (%)                    | 0.285            | 0.167  |
| MCV (fl)                   | 0.484            | 0.014  |
| MCH (pg)                   | 0.249            | 0.230  |
| MCHC (g%)                  | 0.137            | 0.512  |
| Serum iron (µg/dl)         | 0.783            | <0.001 |
| Ferritin (ng/ml)           | 0.555            | 0.004  |
| TIBC (µg/dl)               | 0.644            | <0.001 |
| Transferrin saturation (%) | 0.088            | 0.676  |
| <b>Group II</b>            |                  |        |
| Age (years)                | 0.038            | 0.864  |
| Hb (g/dl)                  | 0.143            | 0.516  |
| HCT (%)                    | 0.276            | 0.203  |
| MCV (fl)                   | -0.364           | 0.088  |
| MCH (pg)                   | 0.270            | 0.214  |
| MCHC (g)                   | 0.013            | 0.954  |
| Serum iron (µg/dl)         | 0.772            | <0.001 |
| Ferritin (ng/ml)           | 0.542            | 0.008  |
| TIBC (µg/dl)               | 0.205            | 0.349  |
| Transferrin saturation (%) | 0.672            | <0.001 |
| <b>Group III</b>           |                  |        |
| Age (years)                | -0.026           | 0.908  |
| Hb (g/dl)                  | 0.292            | 0.187  |
| HCT (%)                    | 0.346            | 0.115  |
| MCV (fl)                   | 0.180            | 0.423  |
| MCH (pg)                   | 0.339            | 0.122  |
| MCHC (g%)                  | 0.003            | 0.990  |
| Serum iron (µg/dl)         | 0.710            | <0.001 |
| Ferritin (ng/ml)           | 0.414            | 0.055  |
| TIBC (µg/dl)               | -0.358           | 0.101  |
| Transferrin saturation (%) | 0.676            | <0.001 |

Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Hence, combined evaluation of these indices may provide complementary clinical diagnostic IDA among children. In our study, urinary levels of hepcidin showed significant positive correlation with Hb, MCV, MCHC, hematocrit value, serum iron level, ferritin level, and T. Sat ( $P < 0.01$ ) (Tables 3 and 5). In contrast urinary levels of hepcidin showed significant negative correlation with TIBC ( $P < 0.01$ ). These results agreed with Cherian *et al.* [14] who found that a positive correlation exists between urinary hepcidin and Hb, MCV, iron, ferritin, and T. Sat levels. On the contrary, a negative association between urinary hepcidin and transferrin saturation is observed.

## CONCLUSION

Hepcidin is a noninvasive and simple parameter that could be used to predict anemia early, before the appearance of hematological affection. Hepcidin is a promising tool to be added to diagnostic tests for iron status. Measurement of this hormone has the potential to become an important tool for diagnosis and treatment of anemia and diseases caused by iron metabolism disorders. Epidemiological studies are needed to demonstrate the role of hepcidin in differential diagnosis of anemia. Further research is needed to provide more information about the expected role of using hepcidin in the management of IDA.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.



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