Kidney injury in infants and children with iron-deficiency anemia before and after iron treatment

Rasha H. Hassan, Shaimaa M. Kandil, Mayada S. Zeid, Maysaa E. Zakia and Ashraf E. Fouda

ABSTRACT

Background: Our study aimed to investigate the effects of iron-deficiency anemia (IDA) on renal tubular functions before and after iron treatment for infants and children with IDA. We measured urinary levels of two kidney injury markers: neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP).

Material and methods: Thirty-six infants and children with IDA and 20 matched healthy controls were included. We assessed different laboratory parameters, estimated glomerular filtration rate, urinary levels of NGAL, and L-FABP. Urinary kidney injury markers were measured in IDA patients before and after 3 months of oral iron therapy.

Results: IDA patients had significantly higher urinary NGAL and L-FABP levels compared to their healthy controls. After 3 months of oral iron treatment, there was a significant improvement (decrease) in urinary NGAL and L-FABP in infants and children with IDA. Urinary markers returned to normal levels (healthy control levels) in children with IDA, but not for infants with IDA compared to their healthy controls.

Conclusion: Subclinical kidney injury was found in infants and children with IDA. This injury was completely reversible in older children with IDA and partially reversible in infants with IDA after iron therapy. Higher urinary levels of kidney injury molecules in IDA infants after iron treatment are suggestive of more sensitivity of these infants to oxidative stress caused by iron therapy or may be due to the immaturity of the kidney and more damage caused by IDA which may require more time to recover.

KEYWORDS

Kidney injury; iron-deficiency anemia; iron treatment

Introduction

Iron-deficiency anemia (IDA) in children is the most prevalent micronutrient deficiency worldwide. Anemia is prevalent in 43% of children less than four years of age and 50% of anemia is attributable to IDA [1,2]. IDA contributes to childhood morbidity and mortality. It is linked to impaired brain development and cognitive functions [3–5]. IDA causes hypoxia which leads to oxidative stress that affects the brain and other organs such as the liver, the heart, and the kidneys. Tissue hypoxia adversely affects the kidneys early and at a higher hemoglobin concentration [6], and plays a significant role in the pathophysiology of renal injury [7].

New markers are needed to diagnose early kidney injury as serum creatinine does not increase unless at least half of the renal function is lost [8]. Some of these new markers which have shown advantages in diagnosing early kidney injury are neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP) [9].

NGAL is a protein released from injured renal tubular cells into the blood and urine in acute kidney injury (AKI). It is released for a long time before a decrease in the glomerular filtration rate can be observed by ordinary laboratory methods [10–12]. Serum and urinary NGAL is a well established biomarker of AKI [13], and it is used for follow-up of chronic kidney disease in children and adults [14]. L-FABP is produced in proximal tubules of the kidney and liver. It has a protective function. L-FABP in the kidney may prevent tubulointerstitial injury by its anti-oxidant activity [15]. L-FABP is a valid biomarker for the early diagnosis of AKI [16]. Urinary excretion of L-FABP is associated with structural and functional damage of renal tubules and is increased in many kidney diseases [17].

The aim of this study was to investigate the effects of IDA on renal tubular functions before and after iron treatment for infants and children with IDA using the urinary levels of NGAL and L-FABP.

Patients and methods

This study was a case–control prospective study. Thirty-six children with IDA were prospectively included. Patients were selected from outpatient clinics of
Mansoura University Children Hospital. All patients were diagnosed with nutritional IDA. A control group of 20 age- and sex-matched healthy children were studied.

Patients were diagnosed with IDA when they have the following: hemoglobin level of <11 g/dl (children aged 6 months–5 years), <11.5 g/dl (children aged 5–7 years) and <12 g/dl (children aged 8–12 years), and decreased mean corpuscular volume in association with iron deficiency. Iron deficiency is defined as serum ferritin level of <12 μg/l (children aged <5 years) or <15 μg/l (children >5 years), or as transferrin saturation <16% [18].

Excluded patients were those who received iron treatment or any nephrotoxic drugs before baseline investigations or children with a disease that may affect the renal functions such as urinary tract infection, diabetes, or any renal, hepatic, cardiac, or pulmonary diseases. Patients with different types of hemoglobinopathy were excluded.

After receiving informed consent, urine and blood samples were obtained and iron therapy was initiated for all patients in the form of oral iron treatment (6 mg/kg/day of element iron) for 3 months. For patients, all investigations were repeated after 3 months of iron treatment.

Biochemical analysis

Different laboratory studies were performed including hemoglobin (Hb), iron, ferritin, TIBC (total iron-binding capacity), hemoglobin electrophoresis, serum creatinine, serum electrolytes (sodium, potassium, calcium), and blood glucose. Ten milliliters of urine samples were collected from the patients and controls. The urine samples were tested for urinary tract infection (UTI). If there is no UTI, the urine samples were centrifuged for 3 minutes at 3000 rpm. Centrifuged urine was placed into two separate Eppendorf tubes and stored at −80°C. NGAL and L-FABP levels were measured by enzyme-linked immunosorbent assay (ELISA) method, according to the manufacturer’s instructions (Glory Science Co. Ltd, Del Rio, TX, U.S.A.).

The estimated glomerular filtration rate was calculated using the modified Schwartz formula for children (eGFR = ml/min/1.73 m² = height (cm) × K/serum creatinine (mg/dl); K = 0.45 (in infants) and K = 0.55 (in children). eGFR ranges were considered normal: (50–150 ml/min/1.73 m² for infants) and (90–160 ml/min/1.73 m² for children) [19]. Serum creatinine values were evaluated according to age and sex.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS, Inc., Chicago, IL, U.S.A.) was used for statistical analyses. Quantitative values were presented as mean ± standard deviation (SD), and categorical data were shown as number and percentage. The Student’s t-test or Mann–Whitney U-test was used in independent groups for comparison. Relationships between data were investigated using Pearson or Spearman correlation analyses. A p-value <0.05 was considered statistically significant.

Results

Our study included 36 children (16 males and 20 females) with IDA and 20 healthy age- and sex-matched controls. Patients were divided into two groups according to the age: infant with IDA group ((included children less than 1 year (n = 21)) and older children with IDA group ((included children older than 1 year (n = 15)).

Different demographic, hematological, and laboratory characteristic for patients and controls are shown in Table 1. The mean age of patients in infant with IDA group was 9.76 ± 1.60 months and for their control group was 9.80 ± 1.47 months. For older children with IDA group, the mean age was 73.56 ± 34.68 months and for their control group was 73.2 ± 28.8 months. There were no significant differences in age or sex distribution between patient groups and their control groups.

Serum sodium, potassium, calcium, creatinine, glucose, and eGFR of IDA patients and controls were in the normal range, and there was no significant differences between IDA patients groups and their control groups (p > 0.05) (Table 1).

The IDA patients (infants and older children groups) had significantly lower Hb, iron, ferritin, and transferrin saturation (p < 0.001), and a higher TIBC (p < 0.001) compared with their healthy control groups (Table 1).

Initial urinary levels of NGAL and L-FABP were significantly higher in patients with IDA (p < 0.001 for both markers), also in infants and children groups with IDA compared to their healthy controls (NGAL: p = 0.007; CI(12.29–17.79), L-FABP: p < 0.001; CI(2.64–4.41) for infants with IDA compared to their controls) and (NGAL: p < 0.0001; CI(10.1–15.18), L-FABP: p = 0.003; CI (2.51–4.32) for older children with IDA compared to their controls) (Table 2).

There was no significant difference between infants and older children with IDA groups comparing their initial levels of both markers (NGAL: p = 0.214; CI (-3.41–1.66) and L-FABP: p = 0.68; CI (-0.93–0.90)). After 3 months of iron treatment for all patients, Hb and iron indices improved (mean ± SD): Hb (12.40 ± 0.43 gm/dl), iron (83.33 ± 5.54 μg/l), and ferritin (41.06 ± 4.11 μg/l). There was no significant difference between infants and older children with IDA as regards Hb and iron indices after iron treatment.

Urinary levels of NGAL and L-FABP after iron treatment were significantly lower (improved) in infants
Table 1. Different demographic, hematological, and biochemical characteristics of children with iron-deficiency anemia and the control group.

| Parameter                        | IDA patients (n = 36) | Controls (n = 20) | p   | IDA infant patients (n = 21) | Control infant (n = 10) | p   | IDA older children patients (n = 15) | Controls older children (n = 10) | p   |
|----------------------------------|----------------------|------------------|-----|-----------------------------|------------------------|-----|-------------------------------------|----------------------------------|-----|
| Age (month)                      | 8.25 ± 2.85          | 7.95 ± 2.81      | NS  | 9.76 ± 1.60                 | 9.80 ± 1.47           | NS  | 73.56 ± 34.68                      | 73.2 ± 28.8                      | NS  |
| Sex                              | 16M:20F              | 8M:12F           | NS  | 9 M: 12 F                   | 4 M:6 F               | NS  | 7 M: 8 F                           | 4 M:6 F                         | NS  |
| Hemoglobin (gm/dl)               | 8.84 ± 0.70          | 12.53 ± 0.23     | 0.001 | 8.96 ± 0.67                 | 12.47 ± 0.34          | <0.001 | 8.66 ± 0.72                       | 12.6 ± 0.3                       | <0.001 |
| Serum iron (μg/dl)               | 37.63 ± 6.32         | 82.05 ± 7.11     | <0.001 | 28.38 ± 6.38                | 83.0 ± 8.75           | <0.001 | 36.60 ± 6.29                      | 81.1 ± 5.30                      | <0.001 |
| Ferritin (μg/l)                  | 14.69 ± 2.57         | 41.45 ± 5.33     | <0.01 | 10.76 ± 0.4                 | 40.1 ± 5.30           | <0.001 | 11.60 ± 2.17                      | 42.80 ± 5.28                     | <0.001 |
| TIBC (μg/dl)                     | 394.89 ± 20.71       | 245.95 ± 5.90    | <0.01 | 425.41 ± 22.17              | 254.3 ± 26.8          | <0.001 | 464.13 ± 98.05                    | 247.60 ± 5.12                     | <0.001 |
| Transferrin saturation (%)       | 9.58 ± 1.85          | 33.34 ± 2.74     | <0.001 | 12.3 ± 1.81                 | 33.92 ± 3.15          | <0.001 | 11.6 ± 1.04                       | 27.75 ± 5.27                     | <0.001 |
| Serum creatinine (mg/dl)         | 0.46 ± 0.14          | 0.46 ± 0.13      | NS  | 0.36 ± 0.07                  | 0.36 ± 0.69           | NS  | 0.60 ± 0.09                       | 056 ± 0.09                       | NS  |
| eGFR (ml/min/1.73 m²)            | 97.21 ± 1.49         | 99.05 ± 1.44     | NS  | 93.10 ± 16.26                | 92.89 ± 1.55          | NS  | 102.90 ± 11.05                     | 105.20 ± 17.0                     | NS  |
| Serum glucose (mg/dl)            | 95.86 ± 5.55         | 93.60 ± 5.73     | NS  | 94.42 ± 5.57                 | 93.3 ± 6.2            | NS  | 97.86 ± 5.04                       | 93.90 ± 5.44                      | NS  |
| Serum sodium (mmol/l)            | 136.83 ± 1.49        | 136.25 ± 1.37    | NS  | 136.71 ± 1.45                | 136.1 ± 1.44          | NS  | 137.0 ± 1.10                       | 136.40 ± 1.34                     | NS  |
| Serum potassium (mmol/l)         | 4.3361 ± 0.14        | 4.28 ± 0.15      | NS  | 4.32 ± 0.15                  | 4.28 ± 0.15           | NS  | 4.35 ± 0.13                       | 4.29 ± 0.14                      | NS  |
| Serum calcium (mg/dl)            | 9.62 ± 0.30          | 9.61 ± 0.42      | NS  | 9.56 ± 0.30                  | 9.61 ± 0.27           | NS  | 9.72 ± 0.27                       | 9.56 ± 0.30                      | NS  |
| NGAL initial (μg/l)              | 17.31 ± 3.76         | 3.46 ± 2.51      | <0.001 | 16.94 ± 4.05                | 1.67 ± 0.53           | 0.007 | 17.82 ± 3.11                      | 5.02 ± 2.28                      | <0.001 |
| NGAL after treatment (μg/l)      | 8.91 ± 2.83          | –                | –   | 10.45 ± 2.61                 | –                      | –   | 6.63 ± 0.90                       | –                                 | –   |
| L-FABP initial (ng/ml)           | 3.91 ± 1.31          | 0.44 ± 0.34      | <0.001 | 3.90 ± 1.33                 | 0.35 ± 0.11           | <0.001 | 3.92 ± 1.34                       | 0.50 ± 0.34                      | <0.001 |
| L-FABP after treatment (ng/ml)   | 1.73 ± 1.14          | –                | –   | 2.37 ± 1.11                  | –                      | –   | 0.84 ± 0.29                       | –                                 | –   |

IDA – Iron-deficiency anemia; TIBC – total iron-binding capacity; eGFR – estimated glomerular filtration rate; NGAL – neutrophil gelatinase-associated lipocalin; L-FABP – liver-type fatty acid-binding protein.

NS: not significant (p > 0.05), p is of significance if <0.05.
and children with IDA compared to their initial levels before treatment (p < 0.001). Urinary levels of NGAL and L-FABP returned to normal levels in children with IDA after treatment (levels of healthy control children group), as there was no significant difference comparing both markers in children IDA after treatment and healthy control children levels (p = 0.57 and p = 0.322, respectively). But, infants with IDA still had significantly higher levels of urinary NGAL and L-FABP post-treatment in comparison to their healthy controls levels (p < 0.001 for both markers) (Table 2).

There was a significant correlation between initial urinary NGAL and L-FABP of patients with Hb and different parameters of iron profile (serum iron, ferritin, transferrin saturation). In addition, there was a significant correlation between initial and after treatment levels of both NGAL and L-FABP (Table 3).

### Discussion

Iron-deficiency is the most common cause of anemia in children [20]. The decrease in Hb leads to reduction the tissue oxygenation and hypoxia. The kidneys are very sensitive to hypoxia which is important in the pathophysiology of kidney injury [6].

### Table 2. Comparison of kidney injury markers (NGAL and L-FABP) before and after treatment among IDA infants and older children patients.

|                         | NGAL initial | NGAL after treatment | p*     | L-FABP initial | L-FABP after treatment | p*     |
|-------------------------|--------------|----------------------|--------|----------------|------------------------|--------|
| IDA patients (n = 36)   | 17.31 ± 3.76 | 8.91 ± 2.83          | p < 0.001 | 3.91 ± 1.31 | 1.73 ± 1.14           | p* < 0.001 |
| (mean ± SD)             | 6.97 – 9.81  | 10.45 ± 2.61         | p < 0.001 | 3.90 ± 1.33 | 2.73 ± 1.11           | p* < 0.001 |
| IDA infant patients (n = 21) | 16.94 ± 4.05 | 10.45 ± 2.61         | p < 0.001 | 3.90 ± 1.33 | 2.73 ± 1.11           | p* < 0.001 |
| (mean ± SD)             | CI(4.66–8.13) | CI(1.76–2.79)       |        | CI(1.24–1.82) | CI(2.35–3.80)         |        |
| IDA older children patients (n = 15) | 17.82 ± 3.11 | 6.63 ± 0.90          | p < 0.001 | 3.92 ± 1.34 | 0.84 ± 0.29           | p* < 0.001 |
| (mean ± SD)             | 9.55–12.82   | CI(0.93–0.90)        |        | CI(0.92–1.12) | CI(2.35–3.80)         |        |
| p**                     | p***(0.214)  | p***(0.001)          |        | p***(0.68)   | p***(<0.001)          |        |
|                         | CI(-3.41–1.66) | CI(2.38–3.54)     |        | CI(-1.90–0.90) | CI(0.92–2.12)         |        |

IDA – Iron-deficiency anemia; NGAL – neutrophil gelatinase-associated lipocalin; L-FABP – liver-type fatty acid-binding protein.

p* Comparing levels before and after treatment in the same patients group.

p** Comparing levels between IDA infant patients and IDA older children patients.

P < 0.05 is significant.

Routine laboratory investigations as serum creatinine and eGFR were within the normal ranges with no significant differences between IDA patients and their healthy controls. But, we could detect a significant higher levels of urinary NGAL and L-FABP in IDA infants and children before treatment in comparison to their healthy controls. These findings are suggestive of subclinical injury caused by IDA which could not be detected by routine laboratory investigations. Similar findings were reported by Güneş et al, who found also higher urine levels of early kidney injury molecules (N-acetyl-b-D-glucosaminidase (NAG), human kidney injury molecule (KIM-1), NGAL, and L-FABP) in children with IDA compared to healthy control subjects which could not detected with usual investigations [21]. Also, similar results were found by Yazdani et al. [22], who reported higher NGAL levels in children who had chronic dialysis and iron deficiency. Elevated NGAL and L-FABP levels may be explained by renal damage resulting from chronic hypoxia. Previous studies reported the existence of structural tubular damage and nephrotoxicity in children with IDA. As there was a significant increase in the levels of some of the urinary markers which were indicative of proximal renal tubules structural damage such as microalbuminuria levels and urinary leucine aminopeptidase (LAP) levels [23], fractional excretion of sodium (FENa+) [24,25], and N-acetyl-b-D-glucosaminidase/creatinine (NAG) [25] in the children with IDA in comparison to controls. On the other hand, Altun et al. [26], reported no marked deterioration in proximal renal tubular functions in IDA children measuring urinary NAG levels.

We re-evaluated the urinary levels of NGAL and L-FABP in infants and older children with IDA after receiving oral iron therapy for 3 months and achieving normal hemoglobin levels. Urinary levels of NGAL and L-FABP in infants and children with IDA significantly reduced compared to the initial levels of urinary markers. This improvement may be attributed to the gradual improvement of hypoxia as hemoglobin is rising over a period of 3 months.

### Table 3. Spearman’s correlation coefficients (r) of urinary biomarkers with other variables in iron-deficiency anemia patients.

|                         | NGAL initial | L-FABP initial |
|-------------------------|--------------|----------------|
| Hemoglobin              | r = 0.651    | r = –0.543     |
| p value                 | 0.001        | 0.020          |
| Iron                    | r = –0.480   | r = –0.460     |
| p value                 | 0.030        | 0.034          |
| Ferritin                | r = -0.492   | r = -0.616     |
| p value                 | 0.023        | 0.013          |
| Transferrin saturation  | r = -0.591   | r = -0.785     |
| p value                 | 0.013        | 0.007          |
| L-FABP initial          | r = 0.960    | r = – -        |
| p value                 | <0.001       | 0.01         |
| NGAL after treatment    | r = 0.466    | –              |
| p value                 | 0.033        | –              |
| L-FABP after treatment  | r = 0.123    | r = 0.848      |
| p value                 | 0.356        | <0.001        |

NGAL – neutrophil gelatinase-associated lipocalin; L-FABP – liver-type fatty acid-binding protein.

p < 0.05 is significant.
Kidney injury markers (NGAL and L-FABP) after treatment of IDA returned to normal levels (of healthy controls group) in older children with IDA but were still higher than healthy controls in infants with IDA. We found no significant difference in the kidney injury markers (NGAL and L-FABP) after the treatment of IDA between the older children group and their controls ($p = 0.57$ and $p = 0.322$, respectively). But, infants with IDA group still had a significant higher urinary levels of NGAL and L-FABP in comparison to their healthy controls ($p < 0.001$) for both NGAL and L-FABP. Incomplete recovery of subclinical renal injury after treatment in infants with IDA may be due to the effect of iron therapy. Infants may be more susceptible to the oxidative and/or nitrosative adverse effects caused by iron preparations. Moreover, infants may have difficulty recovering from renal injury faster than do older children. This may be due to more sensitivity of these infants to oxidative stress caused by iron therapy or may be due to the immaturity of the kidney making it more prone to damage caused by IDA which may require more time to recover. Furthermore, iron deficiency during early life can result in multiple organ systems dysfunction, some of which might not recover despite iron replacement [27]. The effect of iron therapy on renal tubular and glomerular function was evaluated by Altun et al. [26], who suggested that ferrous sulfate used in the treatment of IDA may lead to oxidative stress, although there was no proximal renal tubular dysfunction in IDA children. On the other hand, El-Shimi et al. [23] reported that the adverse effect on the kidney functions of 50 patients (6 months–2 years) with IDA was reversed after 3 months of iron therapy. Although oxidative stress due to chronic hypoxia improves in children and infants with IDA with treatment as hemoglobin rises, they are also exposed to oxidative and/or nitrosative stress caused by iron therapy [28].

We found a negative correlation between initial urinary levels of NGAL and L-FABP with Hb, iron, and ferritin levels. This suggests the influence of anemia on urinary injury molecules. There was also a significant positive correlation between NGAL and L-FABP, which is suggesting that these markers are sensitive biomarkers of kidney injury in children with IDA.

**Conclusion**

We found a subclinical renal injury in infants and children with IDA. This injury completely improved in older children with IDA in comparison to infants with IDA after 3 months of iron therapy. Frequent and prolonged follow-up of urinary kidney injury molecule levels over longer periods of time may be required to assess the improvement of this subclinical injury especially in infants with IDA.

**Acknowledgement**

All authors are equally contributed in writing and revising the manuscript.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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