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# Urinary Kidney Injury Molecules in Children with Iron-Deficiency Anemia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** The aim of this study was to investigate the urine levels of human kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP) in children with iron-deficiency anemia (IDA).

**Material/Methods:** Thirty-five children with IDA and 32 matched healthy controls were recruited. We assessed complete blood count, serum iron, iron-binding capacity, ferritin, serum levels of urea, creatinine (Cr), sodium (Na), potassium (K), calcium (Ca), and glucose levels. Estimated glomerular filtration rate (eGFR) was calculated. Urinary NAG, NGAL, KIM-1, and L-FABP were measured and divided by urine creatinine for comparisons.

**Results:** There were no significant differences in serum urea, Cr, or eGFR between the IDA group and the control group ($p>0.05$, for all). IDA patients had significantly higher urine NGAL/Cr, L-FABP/Cr, KIM-1/Cr, and NAG/Cr compared with the control group ($p<0.05$). There were significant negative correlations between hemoglobin, hematocrit, red blood cell count, and urine NGAL/Cr, NAG/Cr, L-FABP/Cr, KIM-1/Cr levels ($p<0.05$).

**Conclusions:** Higher urinary kidney injury molecule levels in IDA patients suggest a possible subclinical renal injury in pediatric IDA patients whose renal functions and serum electrolytes were normal.

**MeSH Keywords:** Anemia, Iron-Deficiency • Early Diagnosis • Kidney Diseases

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## Background

Anemia is characterized by a decrease in the amount of erythrocytes or hemoglobin concentration in the blood [1]. Anemia is seen in all age groups [2]. According to the World Health Organization, 1.62 billion people are affected by anemia [1]. Iron-deficiency anemia (IDA) is responsible for half of all anemia cases [3]. It has been stated that 273 000 individuals die due to iron-deficiency anemia yearly [3].

Iron is transported in the blood by a delivery protein called transferrin and is found in hemoglobin at the highest concentration. Hemoglobin is a protein that delivers oxygen into the tissues of the body. Failure occurs in hemoglobin production and oxygen delivery to tissues in individuals with iron deficiency, causing tissue hypoxia to develop [4].

Kidney injury is one of the major causes of mortality and morbidity [5]. Hypoxia plays a crucial role in the pathogenesis of kidney injury [6,7]. In previous studies, it has been reported that anemia causes tissue hypoxia in kidneys earlier and at a higher hemoglobin concentration than in other organs [8]. Clinically, serum creatinine and blood urea levels are commonly used to diagnose kidney injury. However, a disadvantage is that these parameters are affected by age, sex, muscle mass, dehydration, and drugs. In addition, creatinine level does not increase unless at least half of the renal function is lost [9]. Therefore, new markers are needed to diagnose kidney injury. It has been shown that human kidney injury molecule (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP) have advantages in diagnosing kidney injury [10]. Despite their advantages in detecting early kidney damage, urinary injury molecules have some limitations in their use. For example, despite being a non-specific marker of kidney injury, urinary NAG activity has been found to be altered by endogenous urea, some nephrotoxins, and heavy metals [11]. In addition, increased urinary NAG levels have been reported in a variety of conditions, such as diabetic nephropathy, rheumatoid arthritis, and hyperthyroidism [12]. In a similar manner, increased urinary NGAL has been found in leukocyturia and as a response to systemic stress in the absence of kidney injury. Urinary LFABP levels were found to be increased in patients with septic shock and acute coronary syndrome [13].

Iron-deficiency anemia is a common type of anemia during childhood [14]. In a search of the literature we found no study on the effect of iron-deficiency anemia on kidney function using kidney injury molecules. Thus, the aim of the present study was to determine urine kidney injury molecule levels in order to evaluate subclinical kidney injury in pediatric patients with IDA.

## Material and Methods

### Subjects and demographics

Thirty-five children with IDA, who were admitted to the Dicle University Hospital Department of Pediatrics and were diagnosed with IDA, were prospectively included in the study. The cause of IDA was nutritional iron deficiency in all our patients. The control group consisted of 32 age- and sex-matched healthy patients without anemia, diseases affecting kidney function, or history of long-term drug use or any drug use during the last 2 months. They were admitted to our hospital due to a routine control check-up or preoperative evaluation for minor surgery, such as circumcision or hernia repair.

The following information was recorded at the time of their admission to the pediatric outpatient clinic; age, sex; weight, height, complaints, presence of symptoms, and result of physical examination. We excluded patients taking any drug that potentially affects kidney function, such as non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, or diuretics, as well as children having a disease such as diabetes, rheumatic disease, urinary tract infection, sepsis, hypoxia, or diseases of the liver, kidneys, heart, or lungs. In addition, thalassemia patients were excluded by performing hemoglobin electrophoresis. After receiving informed consent from the patients and their caregivers, urine and blood samples were obtained. Anemia in childhood was defined as a hemoglobin (Hb) concentration below the cut-off levels established by the World Health Organization: <11 g/dl in children aged 6–59 months, <11.5 g/dl in children aged 5–11 years, and 12 g/dl in older children (aged 12–17) [11]. IDA was diagnosed when the serum iron level was <60 microgram/dL (N=60–150 microgram/dL), iron-binding capacity (TIBC) over 360 µg/dL, transferrin saturation <15% (normal 20–50), and decreased serum ferritin <20 µg /L (normal 40–200 µg /L) (12). Transferrin saturation was calculated as ×100 serum iron/iron-binding capacity. After obtaining the necessary blood samples, iron therapy was initiated in all patients.

### Biochemical analysis

The following laboratory studies were performed from the subjects' blood samples at the time of their admission to the hospital: complete blood count (CBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), and mean corpuscular volume (MCV). We also performed the following biochemical analyses: serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, calcium, glucose, iron, TIBC, ferritin, C-reactive protein (CRP), and hemoglobin electrophoresis. Biochemical analyses were performed photometrically using an Abbott ARCHITECT C16000 analyzer device (Abbott Park, IL). We collected 10-ml urine samples





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**Table 1.** Demographic and biochemical characteristics of children with iron deficiency anemia and the control group.

| | IDA patients (n=35) (mean ±SD) | Controls (n=32) (mean ±SD) | p |
|---|---|---|---|
| Age, years | 5.6±4.0 | 5.8±2.6 | NS |
| Serum glucose (mg/dL) | 90.5±10.9 | 88.6±7.5 | NS |
| Serum urea (mg/dL) | 21.3±9.5 | 24.5±4.8 | NS |
| Serum creatinine (mg/dL) | 0.45±0.11 | 0.39±0.97 | NS |
| Serum sodium (mmol/L) | 137.2±2.6 | 136.1±2.9 | NS |
| Serum potassium (mmol/L) | 4.47±0.43 | 4.28±0.59 | NS |
| Serum calcium (mg/dL) | 9.70±0.44 | 9.78±0.49 | NS |
| CRP | 0.42±0.03 | 0.44±0.20 | NS |
| eGFR (ml/min/1.73 $m^2$) | 107.1±11.5 | 106.3±9.9 | NS |
| Serum iron (µg/dL) | 36.6±21.7 | 72.9±12.6 | <0.001 |
| TIBC (µg/dL) | 412.8±45.4 | 255.8±33.2 | <0.001 |
| Ferritin (µg /L) | 16.3±3.3 | 37.2±10.2 | <0.001 |
| Transferrin saturation (%) | 12.2±2.7 | 29.3±7.4 | <0.001 |

IDA – Iron deficiency anemia; TIBC – total iron binding capacity; eGFR – estimated glomerular filtration rate; SD – standard deviation.

from the subjects. The urine samples were tested for urinary tract infection. The urine samples, collected from the patients who did not have a urinary tract infection, were centrifuged for 3 minutes at 3000 RPM. Centrifuged urine was placed into 4 separate Eppendorf tubes and stored at -80$^0$C. Afterwards, the following variables of urine were measured: creatinine (Cr), NAG, NGAL, KIM-1, and L-FABP levels. These variables were measured by enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's instructions.

The estimated glomerular filtration rate (eGFR) was measured by using the modified Schwartz formula for children. Values of eGFR (mL/min/1.73 $m^2$)=height (cm) ×0.413/serum creatinine (mg/dL). eGFR >90 mL/min/1.73 $m^2$ were considered normal, while eGFR <90 mL/min/1.73 $m^2$ values were considered as decreased kidney function. Serum creatinine values were evaluated according to age and sex.

The study was approved by the Institutional Ethics Board of Dicle University Hospital (02/11/2011-298).

### Statistical analysis

SPSS (Statistical Package for Social Sciences) version 18.0 for Windows (SPSS, Inc., Chicago, IL) was used for statistical analyses. Quantitative values are presented as mean plus/minus standard deviation or median and range, and categorical data are shown as number and percentage. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normally distributed. The Student's *t* test or Mann-Whitney U test was used in independent groups for comparison. The chi square test was used to compare categorical data. Relationships between data were investigated by using Pearson or Spearman correlation analyses. A P value below 0.05 was considered statistically significant.

## Results

This study included 35 children (22 males and 13 females) diagnosed with iron-deficiency anemia (IDA), and 32 healthy children (18 males and 14 females) in the control group. The mean age of patients was 5.63±3.96 years, and that of the control group was 5.84±2.60 years. There were no significant differences in mean age or sex distribution between IDA and control groups (p=0.6307; p=0.434, respectively).

Serum sodium, potassium, calcium, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, and CRP of patients and control subjects were in the normal range, with no significant differences between IDA and control groups (p>0.05) (Table 1). In addition, GFR was in the normal range in IDA subjects and in the control group, with no significant difference found between the 2 groups (p>0.05) (Table 1).





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**Table 2.** Hematological characteristics of iron deficiency anemia and the control group (Mean ± standard deviation).

| | IDA patients (n=35) | Controls (n=32) | P value |
|---|---|---|---|
| Hemoglobin (g/100 ml) | 9.80±2.27 | 13.56±0.71 | <0.001 |
| Hematocrit (%) | 30.71±5.37 | 40.5±3.05 | <0.001 |
| RBC (×$10^6$ cells/μL) | 3.13±0.68 | 5.01±0.58 | 0.007 |
| MCV (fL) | 60.9± 4.85 | 80.5±0.81 | <0.001 |
| PLT (×$10^3$ cells/μL) | 405.6± 143.4 | 306.2± 106.6 | 0.009 |

IDA – iron deficiency anemia; RBC – red blood cells; MCV – mean corpuscular volume; PLT – platelet.

**Table 3.** Comparison of urinary levels of kidney injury molecules in iron deficiency anemia and the control group [Median (minimum–maximum)].

| | IDA patients (n=35) | Controls (n=32) | P value |
|---|---|---|---|
| NGAL/Cr | 12.7 (1.54–85.2) | 3.97 (1.11–10.45) | 0.037* |
| NAG/Cr | 0.25 (0.05–5.31) | 0.20 (0.04–0.36) | 0.032* |
| L-FABP/Cr | 1.55 (0.34–19.2) | 0.91 (0.34–2.09) | 0.020* |
| KIM-1/Cr | 0.549±0.084 | 0.014±0.008 | 0.008** |

IDA – iron deficiency anemia; KIM-1 – human kidney injury molecule; NGAL – neutrophil gelatinase-associated lipocalin; NAG – N-acetyl-β-D-glucosaminidase; L-FABP – liver-type fatty acid-binding protein; Cr – creatinine; SD – standard deviation; * by Mann-Whitney U test; ** by Student's t test.

The IDA group had significantly lower iron, ferritin, and transferrin saturation (p<0.001; p<0.001; p<0.001, respectively), and higher iron-binding capacity (p<0.001) compared with the healthy control subjects (Table 1). RBC, Hb, Hct, and MCV levels were significantly lower in the IDA group compared with the control subjects, whereas the platelet number was significantly higher in IDA children (p=0.007; p<0.001; p<0.001; p<0.001; p=0.009) (Table 2).

Significantly higher urine NGAL/Cr, L-FABP/Cr, KIM-1/Cr and NAG/Cr ratios were found in the IDA group compared to the control group (p=0.037; p=0.020; p=0.008; p=0.032, respectively) (Table 3). Significant negative correlations were found between Hb, Hct, and urinary NGAL/Cr, NAG/Cr, L-FABP/Cr, and KIM-1/Cr ratios (Table 4). In addition, NGAL/Cr, NAG/Cr, L-FABP/Cr, and KIM-1/Cr ratios had significant positive correlations among themselves (Table 4).

## Discussion

We found higher urine levels of early kidney injury molecules (NAG, KIM-1, NGAL, and L-FABP) in children with IDA compared to healthy control subjects. In addition, significant negative correlations were found between hemoglobin, hematocrit, red blood cell count, and urine NGAL/Cr, NAG/Cr, L-FABP/Cr, and KIM-1/Cr levels. These results suggest that IDA can affect the kidneys.

Anemia is a common disease in children. Although there are various types of anemia, iron-deficiency is the most common cause of anemia in childhood. Iron-deficiency anemia can affect functions of many organ systems, especially neurocognitive functions. One of the functions of iron in the human body is to deliver oxygen throughout the body by using the structure of hemoglobin [15]. Iron is transported through the protein transferrin in the blood and is found mostly in the form of hemoglobin. The most important function is iron binding oxygen reversibly on the center of "heme", a protein transferring oxygen in the body. Four iron ions are needed for each hemoglobin unit, located in the structure of each unit of hemoglobin heme binds as a tetramer. This last phase in the formation of hemoglobin cannot occur in the case of iron deficiency and not enough heme can be produced. When there is heme deficiency, globin biosynthesis is automatically suppressed, along with the effectiveness of heme-regulated transcriptional inhibitor (HRI). HRI activity, increasing as a direct result of heme deficiency, suppresses the synthesis of the globin. In addition, it





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**Table 4.** Spearman's correlation coefficients (r) of urinary novel biomarkers with other variables in iron deficiency anemia group.

| | | NGAL/Cr | NAG/Cr | L-FABP/Cr | KIM-1/Cr |
|---|---|---|---|---|---|
| RBC | r | –0.350 | –0.363 | –0.378 | –0.379 |
| | p value | 0.011 | 0.008 | 0.005 | 0.005 |
| Hemoglobin | r | –0.399 | –0.331 | –0.384 | –0.375 |
| | p value | 0.003 | 0.014 | 0.004 | 0.005 |
| Hematocrit | r | –0.382 | –0.330 | –0.385 | –0.375 |
| | p value | 0.005 | 0.015 | 0.004 | 0.005 |
| MCV | r | –0.134 | –0.016 | –0.060 | –0.053 |
| | p value | 0.338 | 0.907 | 0.664 | 0.702 |
| NGAL/Cr | r | | 0.986 | 0.984 | 0.979 |
| | p value | | < 0.001 | < 0.001 | < 0.001 |
| NAG/Cr | r | | | 0.978 | 0.970 |
| | p value | | | < 0.001 | 0.000 |
| L-FABP/Cr | r | | | | 0.992 |
| | p value | | | | < 0.001 |

IDA – iron deficiency anemia; RBC – red blood cells; MCV – mean corpuscular volume; KIM-1 – human kidney injury molecule-1; NGAL – neutrophil gelatinase-associated lipocalin; NAG – n-acetyl-β-D-glucosaminidase; L-FABP – liver-type fatty acid-binding protein; Cr – creatinine.

leads to suppression of the heme transcription initiator, which is a key factor in the synthesis. Ultimately, hemoglobin cannot be formed and anemia develops as a consequence of the suppression of the heme with globin synthesis [16]. Oxygen delivery to the tissue is affected by the Hb concentration in the blood. The decrease in Hb reduces the tissue oxygenation and leads to hypoxia. Hypoxia affects the brain, liver, and, especially, the heart. Since the kidneys are very sensitive to hypoxia, low oxygen pressure in the blood plays an important role in the pathophysiology of kidney injury. Although anemia causes the destruction of tubulointerstitial cells by stimulating hypoxia and leading to acute kidney injury [17], the effect of IDA on the kidneys may be due to chronic hypoxia.

Previous studies have suggested that anemia increases the release of cytokines, such as hypoxia-inducing factor and neuronal nitric oxide synthase, by causing renal hypoxia. In addition, it boosts the sympathetic activity, which decreases glomerular filtration rate and renal blood flow over time in persistent anemia [18]. In our study we found no difference in eGFR between IDA patients and healthy subjects; therefore, we think that the increased kidney injury molecules of IDA found in our study are not related to altered renal blood flow or glomerular filtration.

Serum creatinine level is the most frequently used parameter in renal insufficiency. However, as long as the renal function only deteriorates up to a certain level, serum creatinine levels do not increase. Increasing serum levels lead to an increase in mortality and morbidity rates, depending on the delay in diagnosis and treatment of kidney damage, as kidney function is seriously affected [9]. In previous studies, many compounds have been evaluated for their ability to reveal kidney injury before renal function seriously deteriorates. Some recent studies have suggested that new markers, such as NAG, NGAL, KIM-1, and L-FABP, may be useful in preventing kidney damage [10].

In our study, we found serum urea, creatinine, sodium, potassium, calcium, and GFR values were within normal ranges in the IDA group. Serum electrolyte levels and eGFR did not differ between the IDA group and the control group. Therefore, we suggest that iron-deficiency anemia does not lead to overt kidney injury, as detected by the above-mentioned tests.

RBC, Hb, Hct, MCV, iron, ferritin levels, and transferrin saturation in the IDA group were lower, while iron-binding capacity was higher in the IDA group. The first sign of iron deficiency is the decrease in iron stores, which is determined by low serum ferritin levels. Therefore, the serum ferritin decreases and serum iron declines. Anemia develops in the last phase. The low hematological parameters of the IDA group in the present study are a common characteristic of IDA.





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In this report, urinary NGAL/Cr, NAG/Cr, L-FABP/Cr, and KIM-1/Cr levels, which are known as markers of kidney injury, and whose concentrations in urine increase with slight damage, were found to be significantly higher in the IDA group than in the control group. Therefore, we suggest that IDA causes mild kidney injury, which can only be determined by urinary markers of kidney damage.

Neutrophil gelatinase-associated lipocalin is a 25-kDa transporter protein that is a member of the lipocalin family. It is secreted from epithelial cells and neutrophils, including renal proximal tubule cells. It has been reported that this protein is excreted from kidney tubule cells in the early phase after renal ischemia or administration of nephrotoxic agents, and its level increases in the proximal tubule [19].

In this study, a significant increase was found in the urine NGAL level of the IDA group compared with the control group. We think that this increase is caused by the damage to the kidney tubule cells as a result of chronic hypoxia. NGAL level was found to be elevated in a study of children who had chronic dialysis and iron deficiency [20]. Elevated NGAL levels were also found in children with thalassemia [21]. There were increases in NGAL levels in both studies, depending on renal damage resulting from chronic hypoxia. Additionally, it has been suggested that NGAL had an impact on the maturation of erythrocytes, while increased levels of NGAL inhibit the maturation of erythrocytes and contribute to anemia development.

NAG is a lysosomal enzyme present in the proximal tubule cells. The concentration of this enzyme in urine increases when tubular damage occurs [22]. In our study, there was also a significant increase in urinary NAG/Cr in the IDA group compared to the control group. We think that this increase originates from the damage from hypoxia. In previous studies, it has been reported that NAG increases in cases of deteriorating kidney functions [23,24].

KIM-1 is a type-1 transmembrane glycoprotein. It is expressed at high levels in proximal tubule cells after renal ischemia or administration of nephrotoxic agents. KIM-1 was suggested to be a useful marker in showing damage to proximal tubule cells [25]. Furthermore, a significant increase in KIM-1 levels has been reported in patients having cardiac surgery and in patients taking nephrotoxic agents [22,26], and it has been stated that this reflects the clinical situation as well. The KIM-1 levels were significantly higher in the IDA group compared to the control group in the present study.

L-FABP is a 14-kDA protein and is important in demonstrating parenchymal kidney damage and kidney dysfunction. It is filtered by glomerular filtration and is absorbed in the proximal tubules. Its secretion in the proximal tubule increases after kidney injury [27,28]. It has been found that the amount present in the urine increases after acute tubular necrosis, sepsis, nephrotoxic agents, and cardiac surgery [27,29–31]. In our study, the level of L-FABP was also found to be higher in the IDA group than in healthy controls, probably related to chronic hypoxia.

A negative correlation was found between Hb, Hct, and RBC levels and urinary KIM-1, NGAL, NAG, L-FABP-to-creatinine ratios. This indicates that when anemia worsens, the influence of anemia on urinary injury molecules increases. There were also significant positive correlations among NGAL/Cr, NAG/Cr, L-FABP/Cr, and KIM-1/Cr themselves; thus, it is suggested that these 4 markers have parallel changes in terms of the biomarkers of kidney injury in children with IDA.

An important limitation of our study is that we were not able to study the urine markers after the treatment of IDA, due to the discharge of IDA patients after recovery. This limitation was partially resolved by comparison with the control group.

## Conclusions

The results of this preliminary investigation suggest that patients with IDA may have renal injury determined by urinary kidney injury markers, including KIM-1, NGAL, and L-FABP. Reduced oxygen delivery to kidneys and altered cell function due to anemic hypoxia may be key factors. Further studies are needed to determine the mechanism of kidney injury in IDA.

### Conflict of interest

The authors declare they have no conflicts of interest.

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