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# The role of urinary kidney injury molecule-1 in monitoring the child with idiopathic microscopic hematuria

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**Ethics Committee Approval**
Ethics approval was obtained from the local ethics committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital (Approval date: 23 May 2011, Number: 2011/06-09).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Idiopathic microscopic hematuria is common during childhood, and numerous factors play a role with varying degrees in its etiopathogenesis. We aimed to investigate whether urinary kidney injury molecule-1 level could be a new indicator to detect a possible renal injury that may cause idiopathic microscopic hematuria.

**Methods:** This prospective case-control study included 38 children between 1-15 years of age who were followed up due to idiopathic microscopic hematuria without hypertension and/or edema and 39 healthy individuals with similar gender distribution. Kidney injury molecule-1, urine culture, microalbumin, calcium, magnesium, uric acid, and creatinine levels in spot urine were measured in both groups. A throat culture and abdominal ultrasound were performed on all those included.

**Results:** No significant differences were found between the patient and control groups in terms of age, gender, weight, and height ($P>0.05$). Microalbumin, microalbumin to creatinine ratio in spot urine, urinary kidney injury molecule-1 levels, and kidney injury molecule-1 to creatinine ratio were higher among the patients than the controls ($P=0.016$, $P=0.013$, $P=0.001$, and $P=0.001$, respectively).

**Conclusion:** Urinary microalbumin and kidney injury molecule-1 levels, as well as rates of these two markers to creatinine, may be higher in the children with idiopathic microscopic hematuria. Our findings show that children with microscopic hematuria should be monitored for renal tubular injury and the development of chronic renal disease.

**Keywords:** Idiopathic microscopic hematuria, Kidney injury molecule-1, Microalbuminuria

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## Introduction

Hematuria refers to finding erythrocytes in the urine. This disorder may be visible, as in macroscopic hematuria, or detected by urine analysis, as in microscopic hematuria. Idiopathic microscopic hematuria (IMH) is not associated with any underlying pathology. The prevalence of pediatric hematuria ranges between 1-2% [1]. Persistent asymptomatic IMH was diagnosed in 3690 of 1,203,626 (0.3%) eligible young adults and adolescents [2]. However, hematuria may be one of the early symptoms of renal and systemic pathologies, and in some cases, early diagnosis of the underlying disease may alter its course, such as in acute glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, hypercalciuria, nephrolithiasis, congenital renal abnormalities, Alport Syndrome, and urinary tract infection [3-5].

Classically, IMH is considered a benign disease associated with glomerular diseases. However, the latest data obtained from clinical and experimental studies demonstrate the negative role of glomerular hematuria on renal disease [6, 7]. Hematuria may cause progression to chronic renal disease through glomerular and/or tubular damage [8, 9]. If microscopic hematuria accompanies macroscopic hematuria, the probability of developing chronic kidney disease increases [8, 10, 11].

Biological markers that may be measured objectively show normal or pathological processes. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is produced in proximal tubular cells of the kidney in ischemic and nephrotoxic acute kidney injury (AKI) [11-15]. Some manuscripts report that KIM-1 is a "scavenger receptor" in renal epithelial cell assigned to collect apoptotic material from the tubular lumen [16-18]. The extracellular part of this transmembrane protein is broken down proteolytically and may be detected in the urine. The soluble KIM-1 protein that may be measured in the human urine is approximately 90 kDa [3, 19-21].

In this study, we measured the level of KIM-1, produced by renal tubular cells, which is considered to show a risk of progression to chronic kidney failure in children with IMH. We aimed to detect whether this molecule could determine the prognosis of IMH in terms of renal tubular and/or glomerular damage when compared with healthy children and compared microalbuminuria and KIM-1 for showing their effects on renal progression.

## Materials and methods

### Study design and participants

This prospective case-control study was performed in the Pediatric Nephrology outpatient clinic between March 2011 and February 2012. Before the study, approval was obtained from the local ethics committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital on 23 May 2011 with the number 2011/06-09. Written informed consent forms were obtained from the patient, and the patient's mother and/or father, after thorough information was given about the aim and scope of the study, which was in line with principles of the Helsinki Declaration. The number of children to be included in each group was calculated with a confidence interval of 95% and a power of 90% by the G-Power 3.1 program. Thirty-eight patients and 39 healthy, age-matching controls were enrolled. The patient group included 25 females and 13 males, whereas the control group consisted of 25 females and 14 males. The patients were randomly selected from those who were referred to the Pediatric Nephrology outpatient clinic with incidentally detected microscopic hematuria. The inclusion criteria were an absence of renal pathology and being followed up with IMH for at least four years. The patients with urinary tract infections, urinary tract stones, those with congenital anomalies of the urinary system Alport Syndrome, IgA nephropathy, nutcracker syndrome, a history of Henoch-Schoenlein Purpura, hypertension, proteinuria, or glomerulonephritis were excluded from the study.

### Laboratory studies

After detailed medical history was obtained, urine culture, a full urine analysis, spot urine biochemistry, hemogram, erythrocyte sedimentation rate (ESR) and biochemical analysis of the blood, parathormone, ferritin, complement 3 (C3), C-reactive protein (CRP), anti-streptolysin O (ASO) tests, throat culture analyses as well as renal ultrasound scans were performed, and reports were reviewed and recorded. First and mid-stream urine samples were obtained to evaluate the association of KIM-1 levels with IMH. The urine sample collected was centrifuged at 4,000 rpm for 10 minutes and the supernatant was transferred into the tubes and stored at (-80°C) until analysis. After collection of all samples, KIM-1 levels were measured by quantitative sandwich enzyme immunoassay technique through human urinary TIM-1/KIM-1/HAVCR Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA). The results were recorded in ng/dL. Creatinine levels were also analyzed in the same urine sample. KIM-1 was proportioned to creatinine and expressed in ng/mg creatinine.

### Statistical analysis

SPSS 23.0 package program was used for the statistical analysis of the data. Along with descriptive statistical methods (mean, standard deviation, median, interquartile range), the Mann-Whitney-U test was used to compare binary groups, the independent t-test was used to compare binary groups with normal distribution, and the chi-square test was used for the comparison of qualitative data. The area under the ROC curve was calculated for different cut-offs for KIM-1, and the sensitivity, specificity, positive predictive value, cut-off, and LR (+) values were found. The results were evaluated at 95% confidence interval and a significance level of $P<0.05$.

## Results

There were no participants with a history of familial hematuria among both the control and the study groups. Similarly, the families of the participants did not have any chronic renal disease, or deafness and loss of vision, which may be associated with Alport Syndrome. Ultrasound findings of the urinary system were normal in all cases. Demographic data and blood pressure levels of the cases enrolled in the study were presented in Table 1. There were no significant differences between the two groups in terms of gender distribution, mean age, height, and body weights ($P=0.877$, $P=0.880$, $P=0.227$ and $P=0.152$, respectively). Their mean systolic and diastolic blood pressures were also similar ($P=0.147$ and $P=0.345$, respectively).

Table 1: Demographic data and clinical characteristics of the patient and control groups

| Parameters | | Patients (n=38) | Controls (n=39) | *P*-value |
|---|---|---|---|---|
| Gender | Male n (%) | 13 (34.21) | 14 (35.90) | 0.877 |
| | Female n (%) | 25 (65.79) | 25 (64.10) | |
| Parameters | | Mean (SD) | Mean (SD) | *P*-value |
| Age (years) | | 8.47 (3.46) | 8.36 (3.18) | 0.880 |
| Height (cm) | | 124.69 (31.44) | 131.59 (16.11) | 0.227 |
| Body weight (kg) | | 37.06 (26.06) | 30.54 (10.53) | 0.152 |
| SBP (mmHg) | | 100.66 (11.52) | 104.74 (12.87) | 0.147 |
| DBP (mmHg) | | 60.92 (8.29) | 59.36 (5.98) | 0.345 |

SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

The blood tests performed to exclude the causes of hematuria in the patients were presented in Table 2. Blood hemoglobin levels were significantly lower in the patient group when compared with the control group ($P$=0.049). However, the two groups were similar with regards to leukocyte and platelet count, prothrombin time, activated partial thromboplastin time, urea, and C3 levels ($P$>0.05). CRP levels were significantly higher in the patient group than the control group ($P$=0.028); while ESR, uric acid, creatinine, calcium, ASO, parathormone, and ferritin levels were similar ($P$>0.05).

This study mainly focused on the urine analysis findings, which were shown in Table 3. While the mean urine pH, calcium, uric acid, magnesium levels, creatinine, uric acid to creatinine, and magnesium to creatinine rates in spot urine were similar between the two groups ($P$=0.214, $P$=0.818, $P$=0.804, $P$=0.307, $P$=0.051, $P$=0.203, and $P$=0.945, respectively), the mean urine density, erythrocyte count, spot urine microalbumin level, microalbumin to creatinine rate, KIM-1 level, and KIM-1 to urine creatinine ratio of the study group were significantly higher compared to those of the control group ($P$=0.003, $P$=0.001, $P$=0.016, $P$=0.013, $P$=0.001, and $P$=0.001, respectively).

Table 2: Comparison of blood analysis findings in the patient and control groups

| Parameters | Patients (n=38) Mean (SD) | Controls (n=39) Mean (SD) | *P*-value |
|---|---|---|---|
| Hemoglobin (gr/dL) | 12.03 (0.75) | 12.39 (0.85) | 0.049 |
| Leukocyte ($mm^3$) | 7.91 (2.49) | 8.45 (3.5) | 0.438 |
| Platelets ($mm^3$) | 282.89 (75.15) | 315.03 (91.87) | 0.098 |
| Prothrombin time (sec) | 12.67 (3.28) | 11.9 (0.84) | 0.164 |
| aPTT (sec) | 33.56 (11.2) | 31.91 (6.88) | 0.438 |
| Complement 3 (mg/dL) | 128.93 (23.12) | 129.09 (24.64) | 0.978 |
| Parameters | Median (min-max) | Median (min-max) | *P*-value |
| Uric acid (mg/dL) | 3.3 (2.18-4.05) | 3.4 (2.7-3.8) | 0.748 |
| Creatinine (mg/dL) | 0.5 (0.43-0.54) | 0.5 (0.4-0.5) | 0.347 |
| Calcium (mg/dL) | 4.25 (2.3-9) | 6.2 (2.3-10.3) | 0.727 |
| ESR (mm/h) | 16 (4.25-28) | 12 (2-18) | 0.247 |
| ASO (U/mL) | 182.4 (37.73-299.58) | 140 (45.1-212.8) | 0.173 |
| CRP (mg/dL) | 0.14 (0.06-0.76) | 0.05 (0.03-0.25) | 0.028 |
| PTH (pg/mL) | 25.2 (17.33-42.4) | 29.3 (20.8-41.8) | 0.386 |
| Ferritin (ng/mL) | 30.1 (21.31-47.55) | 26.9 (14.06-36.37) | 0.137 |

SD: Standard deviation, aPTT: Activated partial thromboplastin time, ESR: Erythrocyte sedimentation rate, ASO: Anti-streptolysin O, CRP: C-reactive protein, PTH: Parathyroid hormone

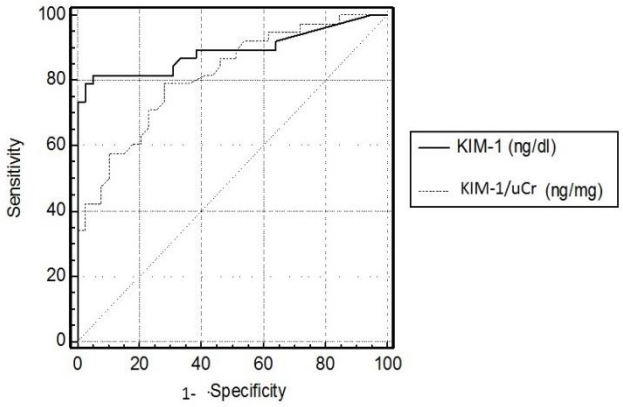
Table 3: Comparison of urine microscopy and biochemical findings between the patients and controls

| Parameters | Patients (n=38) Mean (SD) | Controls (n=39) Mean (SD) | *P*-value |
|---|---|---|---|
| pH | 5.71 (0.65) | 5.92 (0.85) | 0.214 |
| Density | 1019.32 (5.91) | 1014.67 (7.08) | 0.003 |
| Erythrocyte/per area (count) | 134.68 (55.79) | 1.77 (1.27) | 0.001 |
| Parameters (In spot urine) | Median (min-max) | Median (min-max) | *P*-value |
| uCr (mg/dL ) | 73.53 (13.4-156.00) | 89.35 (21.20-184.00) | 0.113 |
| uCa (mg/dL) | 7.21 (2.30-15.00) | 7.39 (2.80-18.00) | 0.818 |
| uCa/uCr (mg/mg Cr) | 0.15 (0.02-0.47) | 0.10 (0.03-0.25) | 0.051 |
| uUA (mg/dL) | 50.02 (24.00-85.00) | 50.87 (24.00-85.00) | 0.804 |
| uUA/uCr (mg/g Cr) | 1.07 (0.15-3.97) | 0.82 (0.22-3.30) | 0.203 |
| uMA (mg/dL) | 10.74 (2.00-36.90) | 6.92 (2.10-14.00) | 0.016 |
| uMA/uCr (mg/mg Cr) | 0.19 (0.02-0.81) | 0.10 (0.02-0.49) | 0.013 |
| uKIM-1 (ng/dL) | 165 (106.5-201.8) | 36 (15-72) | 0.001 |
| uKIM-1/uCr (ng/mg Cr) | 1.47 (0.89-2.61) | 0.59 (0.32-1.0) | 0.001 |

SD: Standard deviation, Ca: Calcium, Cr: Creatinine, UA: Uric acid, MA: Microalbumin, uKIM-1: Urinary kidney injury molecule-1

The ROC analyses of urine KIM-1 and KIM-1 to uCr were reviewed for the differential diagnosis of hematuria. The area under the curve was 0.891 (0.035) for KIM-1 with a cut-off of >92%, a sensitivity of 81.58%, a specificity of 94.87%, a positive predictive value of 93.9%, a negative predictive value of 84.1%, and a positive likelihood ratio (LR+) of 15.91. These results revealed that hematuria probability in a patient with KIM-1 >92% was 15.91-fold of that of a patient with KIM-1 <92%. The area under the curve was 0.815 (0.049) for KIM-1/uCr, with a cut-off of >80%, a sensitivity of 78.95%, a specificity of 71.79%, a positive predictive value of 73.2%, a negative predictive value of 77.8%, and an LR+ value of 2.80. The hematuria probability in a patient with KIM-1 >80 was 2.80-fold of that of a patient with KIM-1 <80% (Figure 1).

Figure 1: Importance of urinary KIM-1 and urinary KIM-1 to urine creatinine ratio for identification of hematuria




## Discussion

We found that uKIM-1 and microalbumin levels in the spot urine as well as these parameters to uCr ratio are higher in children with IMH compared to the control group. However, the elevation in uKIM-1 was more significant than the uMA. As it is non-invasive, we think that performing this test should be considered for IMH monitoring in children.

Although pediatric IMH is mostly associated with benign causes, it may rarely cause chronic kidney damage [5, 8, 11]. We did not perform a renal biopsy on our patients, because it is not the right approach. Renal biopsy is not recommended if there is no suspicion of IgA nephropathy, Alport syndrome, familial thin basement membrane disease, and other glomerulopathies. Demographic data, physical examination findings, blood pressure levels, and laboratory findings of the patients and controls enrolled in the study were normal in both groups and did not significantly differ. Renal function tests were within normal limits. These findings suggest that our patients were unlikely to have any disease other than IMH. However, lower hemoglobin and higher CRP levels in the patient group may be indicative of mild chronic inflammation.

Analysis of spot urine findings of the patient and control groups revealed that urine density and erythrocyte count per area under the microscope were significantly higher in the patient group than in the control group. The lack of significant difference in terms of calcium, creatinine, uric acid, magnesium levels in spot urine shows the absence of various etiological causes of hematuria, including hypercalciuria and hyperuricosuria in our patients. Similarly, there were no significant differences in serum ESH, ASO, parathormone, ferritin, urea, uric acid, creatinine, C3, calcium, phosphor, and alkaline phosphate levels. All these results support the diagnosis

of IMH in our patients. Higher KIM-1 levels, as well as KIM-1 to Cr ratio, indicate that these patients are in the risk group for the progression to chronic kidney diseases. Although serum Cr and cystatin C levels are mainly used to determine this risk, they are increased later than the new biological markers. There are numerous studies conducted on the KIM-1 biomarker in the literature. Significantly higher levels of urine KIM-1 from the first day of AKI diagnosis guide us for the diagnosis and treatment of AKI [12-14, 21-23]. A study conducted on 249 patients diagnosed with AKI detected elevated levels of NGAL, KIM-1, and IL-8 on the first day of diagnosis [24]. Matrix metalloproteinase 3, serum albumin, and TNF have regulatory roles in the release of KIM-1 from proximal tubular epithelial cells [25], and the early elevation in KIM-1, cystatin C, IL-8, and L-FABP levels and dialysis need decrease with early diagnosis [26]. These findings show the necessity of advanced examinations before renal biopsy for assessing the underlying renal pathology in IMH patients with higher urine KIM-1 levels. Children with IMH should be monitored for renal progression.

Higher urine microalbumin, as well as microalbumin to creatinine ratio, support the idea that these patients are in the risk group for the progression of chronic kidney disease. Although serum creatinine and cystatin C levels are mostly used to determine this risk, they increase later than the new biological markers. The effects of microalbuminuria and proteinuria on renal progression are well known [27]. Microalbumin to Cr ratio reflects renal disease progression [28]. For example, persistent MA in urine in Type 1 Diabetes Mellitus patients progresses to end-stage renal disease [29]. Higher MA and KIM-1 levels, and their ratio to creatinine in IMH patients are crucial findings in our study. The elevation in KIM-1 was more significant than that in MA, which shows that IMH patients should be monitored for renal tubular injury and the development of chronic renal disease. The relationship of these two markers with each other should also be emphasized.

**Limitations**

One of the limitations of the present study was the small number of patients. We also could not exclude IgA nephropathy, thin basal membrane disease, and Alport syndrome which are important in the etiology of microscopic hematuria and may only be diagnosed with renal biopsy even medical history and laboratory findings do not match. Therefore, comprehensive studies with more extensive case series should be performed for the association of hematuria and KIM-1.

**Conclusion**

KIM-1, KIM-1/uCr, MA, and MA/uCr can be used to monitor disease progression in IMH. Along with urine microalbumin, the elevation of KIM-1 suggests the necessity of further analysis when hematuria is detected, and it is a non-invasive test that may be used conveniently during follow-up. Slightly higher CRP levels of these patients indicate a persistent inflammation. Blood hemoglobin levels were negatively affected by persistent microscopic hematuria and chronic inflammation. Therefore, patients diagnosed with IMH should be monitored regularly. In this regard, we believe that the problems will be solved better with large series in children with hematuria who underwent renal biopsy.

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