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Research Article

Potential biomarkers in pediatric Familial Mediterranean Fever-related nephropathy: KIM-1 and NGAL

Pediatrik Ailesel Akdeniz Ateşi ilişkili nefropatide potansiyel biyobelirteçler: KIM-1 ve NGAL

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Abstract

Introduction: Familial Mediterranean Fever (FMF) is an autoinflammatory disease which exhibits an autosomal recessive inheritance manner and is characterized by inflammation of serosal membranes including pleurae, synovia, and peritoneum, usually with accompanying fever and pain, and presents with symptomatic episodes. Kidney Injury Molecule-1 (KIM-1) is a novel biomarker of acute renal injury (ARI) which is secreted by the proximal tubule cells after occurrence of kidney damage, which shows tubule damage sensitively and is easily detectable by urinary biochemistry analysis. Neutrophil Gelatinase Associated Lipocalin (NGAL) is a novel biomarker that can be identified in the distal tubules and collecting ducts after development of ARI. Besides some traditional parameters like glomerular filtration rate, there is no specific biomarker to predict kidney injury or failure in FMF. There is very scant data regarding role of NGAL and KIM-1 in predicting FMF-related nephropathy and kidney failure. Our objective was to shed some light on whether urinary KIM-1 and/or NGAL levels can be used as biomarkers of renal injury in FMF patients.

Methods: This prospective study included patients with clinical diagnosis of FMF who were admitted to our Pediatric Emergency Clinic between January 2018 and January 2019, and healthy children of similar gender and age as controls. Urine samples were collected for urinary KIM-1 and NGAL analyses. When a sufficient number of patients were reached, KIM-1 and NGAL levels were measured from the samples. Urinary KIM-1 levels were determined using an ELISA kit. Urinary KIM-1 levels were standardized for urine creatinine (ng/mg). NGAL enzyme activities were measured spectrophotometrically using commercial kits.

Results: A total of 56 children, 51.8% (n=29) Familial Mediterranean Fever patients and 48.2% (n=27) controls, were recruited. Kidney injury molecule-1 levels in pediatric FMF patients were elevated than those noted in the controls (p=0.003), while KIM-1/creatinine ratios were similar (p=0.500). Pediatric FMF patients had elevated NGAL levels than those of the controls (p<0.001). Mean NGAL/creatinine ratio of FMF patients (5.24±4.19) were also higher than that of the control group (0.03±0.03) (p<0.001).

Conclusion: While findings indicating acute tubular damage such as proteinuria and hematuria have not developed, high KIM-1 and NGAL levels may indicate that these biomarkers are likely to be used as reliable, non-invasive, and early predictors of renal injury. Larger multicenter clinical studies are necessary for urinary levels of these molecules to be routinely used for earlier recognition of FMF-related renal injury.

Keywords: Child, Familial Mediterranean Fever, Kidney Injury Molecule-1, Neutrophil Gelatinase-associated Lipocalin

Öz

Giriş: Ailevi Akdeniz Ateşi (AAA), otozomal resesif kalıtım tarzı gösteren ve plevra, sinovya ve periton gibi serozal membranların iltihabı ile karakterize, genellikle ateş ve ağrıya eşlik eden ve semptomatik ataklarla görülen otoinflamatuar bir hastalıktır. Kidney Injury Molecule-1 (KIM-1), böbrek hasarının oluşmasından sonra proksimal tübül hücreleri tarafından salgılanan, tübül hasarını hassas bir şekilde gösteren ve idrar biyokimya analizleriyle kolayca tespit edilebilen akut böbrek hasarının yeni bir biyobelirtecidir. Nötrofil Jelatinaz İlişkili Lipokalin (NGAL), akut böbrek hasarı (ABH) geliştikten sonra distal tübüllerde ve toplayıcı kanallarda tanımlanabilen yeni bir biyobelirteçtir. Glomerüler filtrasyon hızı gibi bazı geleneksel parametrelerin yanı sıra, AAA'inde böbrek hasarını veya yetmezliğini tahmin etmek için spesifik bir biyobelirteç yoktur. NGAL ve KIM-1'in AAA ile ilişkili nefropati ve böbrek yetmezliğini öngörmedeki rolü hakkında çok az veri vardır. Ailesel Akdeniz Ateşi hastalarında üriner KIM-1 ve/veya NGAL düzeylerinin renal hasar biyobelirteci olarak kullanılıp kullanılamayacağını aydınlatmayı amaçladık

Yöntem: Bu prospektif çalışmaya, Çocuk Acil kliniğimize Ocak 2018-Ocak 2019 tarihleri arasında başvuran, klinik olarak AAA tanılı hastalar ile kontrol grubu olarak, cinsiyet ve yaşları benzer sağlıklı çocuklar dahil edildi. Üriner KIM-1 ve NGAL analizleri için idrar numuneleri alındı. Yeterli hasta sayısına ulaşıldığında örneklerden KIM-1, NGAL düzeyleri ölçüldü. Üriner KIM-1 düzeyleri ELISA kiti kullanılarak ölçüldü ve idrar kreatinin (ng/mg) için standardize edildi. NGAL enzim aktiviteleri ticari kitler kullanılarak spektrofotometrik olarak ölçüldü.

Bulgular: Ailesel Akdeniz Ateşi tanılı 29 (%51,8) ve sağlıklı 27 (%48,2) kişi olmak üzere 56 çocuk çalışmaya alındı. KIM-1 düzeylerinin hasta grubunda kontrollere kıyasla artmış olduğu görülürken (p=0,003), KIM-1/kreatinin oranları benzerdi (p=0,500). NGAL düzeyleri ve NGAL/kreatinin oranları, kontrol grubuna (0,03±0,03) kıyasla hasta grubunda (5,24±4,19) daha yüksekti (her ikisi için p<0,001).

Sonuç: Akut tübüler hasarı gösteren proteinüri ve hematüri gibi bulgular gelişmediğinden, yüksek KIM-1 ve NGAL düzeylerinin, renal hasarın güvenilir, noninvaziv ve erken biyobelirteçleri olarak kullanılabileceğine işaret ediyor olabilir. Bu moleküllerin üriner düzeylerinin, AAA ile ilişkili renal hasarın daha erken tanınmasında rutin olarak kullanılabilmesi için daha geniş çok merkezli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ailesel Akdeniz Ateşi, Çocuk, Böbrek Hasarı Molekülü-1, Nötrofil Jelatinaz İlişkili Lipokalin

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Key Points

1. FMF patients had significantly higher KIM-1 levels compared to the controls.
2. KIM-1/creatinine ratio was found similar in patient and control groups (Probably as a result of subsequent increase in creatinine following an increase in KIM-1)
3. FMF patients had significantly higher NGAL level and NGAL/creatinine ratio compared to the controls.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disease which exhibits an autosomal recessive inheritance manner and is characterized by inflammation of serosal membranes including pleurae, synovia, and peritoneum, usually with accompanying fever and pain, and presents with symptomatic episodes [1,2]. The most common symptoms include chest pain, fever, myalgia, abdominal pain, joint pain, myalgia, and erysipelas-like erythema [3]. Among the most significant and frequent complications of FMF is secondary amyloidosis. Despite diagnostic and therapeutic advancements, FMF may result in amyloidosis and, ultimately, renal injury and failure [4]. Colchicine is the fundamental therapeutic modality which is efficacious both in diminishing the frequency of episodes and in preventing development of amyloidosis [5].

Kidney Injury Molecule-1 (KIM-1) is a novel biomarker of acute renal injury which is secreted by the proximal tubule cells after occurrence of kidney damage, which shows tubule damage sensitively and is easily detectable by urinary biochemistry analysis. [6-8]. Neutrophil Gelatinase Associated Lipocalin (NGAL- Lipocalin 2) is a novel biomarker that can be identified in the distal tubules and collecting ducts after development of acute renal injury (ARI) [9-11].

Besides some traditional parameters like glomerular filtration rate, there is no specific biomarker to predict kidney injury or failure in FMF. There is very scant data regarding role of NGAL and KIM-1 in predicting FMF-related nephropathy and kidney failure. This study was conducted to investigate urinary KIM-1 and NGAL levels in order to determine their roles in early recognition of development of nephropathy and to determine their utility for follow-up of progression in pediatric FMF patients.

Methods

Patients who were being followed up for FMF in our hospitals' outpatient pediatric nephrology clinic and admitted to pediatric emergency department due to extrarenal complaints were recruited. Our study was conducted with a prospective design after a local ethics committee approval was obtained and informed consents from parents of patients were taken. All procedures of study were enforced in compliance with the Declaration of Helsinki. Patients diagnosed with any disease that may potentially affect the urinary tract (nephrotic syndrome, chronic renal failure, urinary anomalies, nephrolithiasis, etc.), with a story of recent nephrotoxic drug use, who were having or had recently had an FMF attack, FMF patients with renal involvement and those who denied participation in the study were excluded.

The sample size for the study was calculated using the G*Power program for an independent t-test between two groups. A type I error margin of 0.05, 80% power, and a large effect size (0.8) were used, with the case-to-control ratio set at 1:2. Clinical and demographic features, as well as laboratory data, and organ involvement status of the patients were recorded. Gender-matched and age-matched healthy (without renal, infectious, metabolic, rheumatological disease or any chronic disease) children admitted to the general pediatric outpatient clinic for several reasons (routine control, anemia follow-up, abdominal pain, fatigue, loss of appetite, etc.) for whom urinalysis was requested, comprised the control group.

Spot urine specimens were obtained for measurement of urinary levels of protein, creatinine, KIM-1, and NGAL. The specimens were centrifugated for five minutes at 3000 rpm and obtained supernatants were deposited at -80°C until a collective analysis. KIM-1 and NGAL levels were estimated from the samples, using ELISA test kits (USCN, Wuhan USCN Business Co; ELISA kit product number, SEA785Hu and SEB388Hu). Jaffe method was utilized for measurement of urinary creatinine levels using an autoanalyzer. Levels of these molecules were also represented in proportion to creatinine to standardize and represented as ng/mg creatinine.

Ethical approval, informed consent, and permissions

Ethics Committee title, date, and the number: This study was approved by Necmettin Erbakan University Ethics Committee (Date: 24th May 2019, Decision No: 2019/1898). Informed consent: Informed written consents from the parents were obtained.

Statistical analysis

For data analysis, SPSS 27.0 for Windows (SPSS, Inc., Chicago, IL) package program was used. Data's conformity to normal distribution was examined using visual methods like histograms and probability graphs and analytical methods like Shapiro-Wilk tests. For expression of numeric data, mean±standard deviation and median (minimum-maximum) values were used, whereas counts and percentages were used to express categorical data. Categorical data were compared using Pearson's Chi-Squared ($\chi 2$) test. Independent Sample T test was used for comparison of normally distributed numeric data and categorical data and Mann-Whitney U test for non-normally distributed data. Correlations of non-normally distributed numeric variables were analyzed using Spearman's correlation coefficient. A $P<0.05$ was considered statistically significant.

Results

A total of 56 children, 51.80% (n=29) FMF patients and 48.20% (n=27) controls, were recruited. Of the FMF group, 62.10% (n=18) were female and 37.90% (n=11) male, whereas 51.90% (n=14) were female and 48.10% (n=13) male in the control group. No significant difference in gender distribution was noted (p=0.440). The mean age was 12.81±4.08 years in patients with FMF and 12.29±2.04 years in the controls (Table 1).

Table 1. Gender and age characteristics of the groups

Characteristics		Patient Group (n=29)	Control Group (n=27)
		n (%)	n (%)
Gender	Female	18 (62.10)	14 (51.90)
	Male	11 (37.90)	13 (48.10)
		Mean ± Standard Deviation	Mean ± Standard Deviation
Age (years)		12.81±4.08	12.29±2.04

All recruited FMF patients were determined to be on colchicine treatment, with no biological agents. In FMF patients, mean duration of disease was 6.02±4.0 years, and mean duration of colchicine use was 5.36±4.48 years (Table 2).

Table 2. Characteristics of FMF patients

Characteristics	Patient Group (n=29)	
	Mean±Standard Deviation	Min-Max
Disease Duration (years)	6.02±4.08	0.90-13.00
Duration of Colchicine Use (years)	5.36±4.48	0-13.00

In comparison with the controls, pediatric FMF patients had higher urinary levels of KIM-1 of the pediatric FMF patients (P<0.001), KIM-1/creatinine ratios showed no significant statistical difference (P=0.500). NGAL levels in pediatric FMF patients were demonstrated to be higher than those of the controls (P<0.001). Compared with control group (0.03±0.03), pediatric FMF patients had a higher mean NGAL/creatinine ratio (5.24±4.19) (P<0.001) (Table 3, Figure 1). (Range at 95% CI in patients for KIM-1, KIM-1/creatinine, NGAL, and NGAL/creatinine were 316.31-517.69, 4,32-7.68, 3.04-4.96 and 3.41-6.59, respectively; in the control group, these values were 173.37-294.63, 2.56-7.44, 0.52-1.48 and -0.01-0.01, respectively

Table 3. Comparison of KIM-1, NGAL and their proportions to creatinine between the groups

Parameters	Patient Group (n=29)	Control Group (n=27)	
	Mean±Standard Deviation	Mean±Standard Deviation	p*
KIM-1 (pg/ml)	417.16±264.77	234.70±153.23	**0.003**
KIM-1/creatinine	6.43±4.41	5.45±6.17	0.500
NGAL (ng/ml)	4.06±2.52	1.70±1.21	**<0.001**
NGAL/creatinine	5.24±4.19	0.03±0.03	**<0.001**

*Independent Sample T Test, KIM-1; kidney injury molecule-1, NGAL; Neutrophil Gelatinase Associated Lipocalin

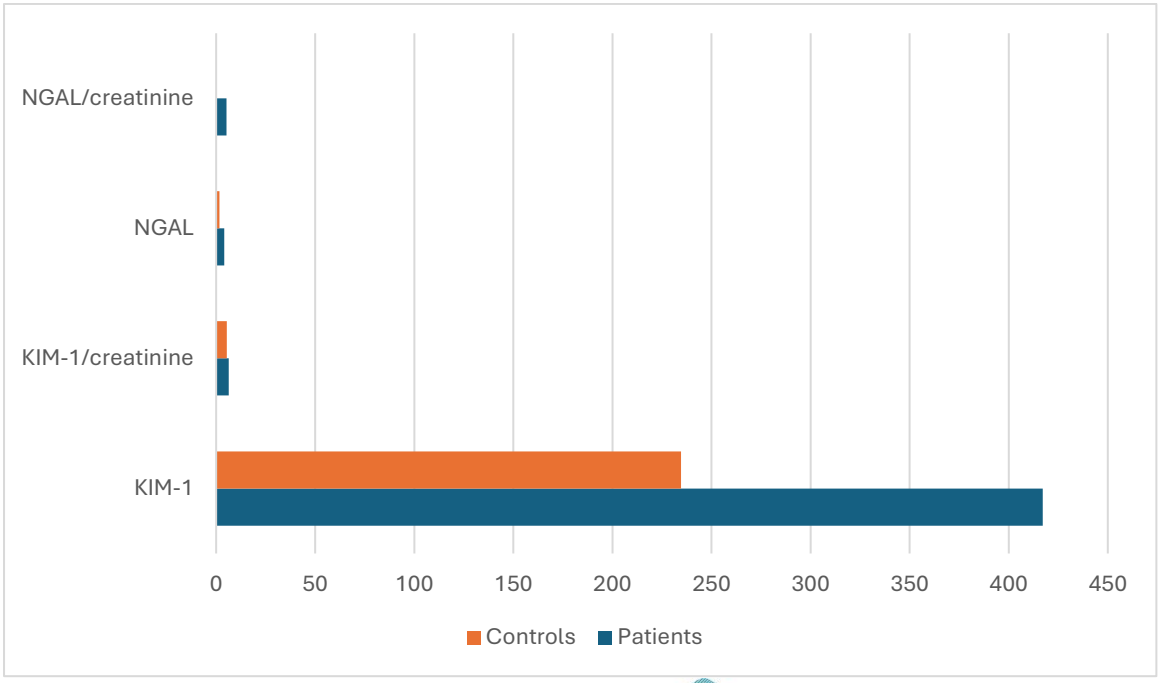


Figure 1. KIM-1, NGAL and their proportions to creatinine

In pediatric FMF patients, no significant correlation of KIM-1 levels, KIM-1/creatinine (KIM-1/crea) and NGAL and NGAL/creatinine (NGAL/crea) ratios with age, disease duration, and duration of colchicine use were found (for all P>0.050) (Table 4). Although urinary levels of KIM-1 and NGAL were found to increase with the duration of disease, this was not statistically significant. Furthermore, we determined a significant positive correlation of creatinine and urea levels with KIM-1 and a significant negative correlation of KIM-1 levels with GFR.

Table 4. Correlation of KIM-1, NGAL and their ratios to creatinine with some characteristics in FMF patients

	KIM-1		KIM-1/creatinine		NGAL		NGAL/creatinine	
	r	p*	r	p*	r	p*	R	p*
Age (years)	-0.127	0.510	0.151	0.435	0.302	0.112	0.176	0.360
Disease Duration (years)	0.009	0.964	-0.100	0.607	0.182	0.345	0.070	0.720
Duration of Colchicine Use (years)	0.065	0.736	0.015	0.940	0.042	0.828	-0.052	0.791

*Spearman's Correlation Test, KIM-1; kidney injury molecule-1, NGAL; Neutrophil Gelatinase Associated Lipocalin

Discussion

Although previous studies reported a male predominance in FMF, classical knowledge involves similar affection of both genders (13,14). In a study examining laboratory, epidemiological and mutational characteristics in pediatric cases of FMF, Solmaz et al. found a M/F ratio of 1.1/1 (15). In consistency with the literature, the male/female ratio was 1.6/1 in our study. However, our sample size is relatively small, which may hinder generalizability of our findings.

In the literature, some studies, and meta-analyses regarding potential role of KIM-1 and NGAL in early recognition of ARI have been conducted (16). Ture et al. compared urinary KIM-1 and NGAL levels and KIM-1/crea and NGAL/crea ratios of Henoch-Schönlein Purpura (HSP) patients with those of the controls, all of which were significantly increased in HSP patients (11). Oksay et al. studied only urinary NGAL levels in their study conducted on children FMF, and they found that FMF patients had significantly higher urinary NGAL levels and NGAL/crea ratios that those of the controls (17). Similarly, our study revealed that pediatric FMF patients had significantly higher KIM-1 and NGAL levels, in addition to significantly higher NGAL/crea ratios ($p<0.05$). Creatinine increases following kidney injury after an increase in KIM-1, which is not observed in healthy controls, which may result in similar ratios by increasing in both KIM-1 and creatinine. Since we do not include pediatric FMF patients with active exacerbations, the effect of exacerbations on levels of KIM-1, NGAL and their proportions to creatinine might differ in such patients.

Since colchicine is the fundamental therapeutic modality and efficacious in both diminishing frequency of episodes and preventing development of amyloidosis (5), in a study by Yildiz et al., colchicine was initiated in all patients and patients' mean follow-up duration was reported as 70.9 months (5.9 years) (18). Likewise, all of our patients were on colchicine treatment, with a mean follow-up duration of 6.02 years.

For detection of acute renal injury, early predictive biomarkers with prognostic properties are essential to guide the disease process and improve outcomes of patients. Serum creatinine remains the gold standard noninvasive biomarker for detecting renal injury, although its sensitivity is low and its level does not increase significantly until renal functions decrease by approximately 50% (19). While acute tubular injury is a histological diagnosis, we could not perform biopsy for majority of the patients, since patients and/or parents denied due to invasiveness of the procedure (20, 21). Thus, multiple studies on novel markers like KIM-1 and NGAL have been conducted within last 20 years (19). Thus, serum creatinine values of patients with FMF-related renal involvement increases when kidney involvement occurs, but it is known that the patient's creatinine status does not contribute to prediction of disease progression of the disease before renal involvement (22). All these indicate the need for newly emerging noninvasive biomarkers for early detection of a pending renal involvement in pediatric FMF.

Ischemic or toxic renal injury is known to trigger KIM-1 secretion (23, 24). Similarly, in a mouse study, marked induction of KIM-1 protein secretion following kidney damage was demonstrated (25). In a study, van Timmeren et al. revealed that various conditions presenting with kidney injury, including hypertension, diabetic nephropathy, FSGS, IgA nephropathy, lupus nephritis, membranous nephropathy, Wegener granulomatosis, and acute allograft rejection, may exhibit up-regulated KIM-1 expression (26). Another study measured urinary and serum KIM-1 levels in biopsy-confirmed acute tubular injury patients and KIM-1 expression was examined from renal biopsy specimens. Based on that, the conclusion was drawn that urinary KIM-1 levels reflect severity of histological renal injury, and that contemporaneous use of serum and serum KIM-1 levels may increase specificity and sensitivity in diagnosing ATI (27).

NGAL is a glycoprotein that is secreted from tubular cells following ischemic or toxic kidney damage. Varying levels of NGAL gene expression have been indicated in other tissues as well, including salivary glands, uterus, trachea, kidney, colon, and prostate (28). Another study analyzed acute kidney failure in animal models so as to examine biomarkers potentially beneficial in clinical settings and for a better understanding of underlying molecular mechanisms of renal injury. NGAL mRNA was determined to be up regulated within a few of hours following renal injury, including those caused by cisplatin nephropathy, renal ischemia, and reperfusion. This has been found to occur before the elevation of traditional markers for renal damage, such as serum creatinine, urinary N-acetyl glucosaminidase, beta-2 microglobulin (29). A previous study reported that, in patients hospitalized for acute tubular injury, NGAL levels were much higher in the beginning and then rapidly decreased. It was concluded that NGAL measurements should be performed as early as possible (30). In our study, the high values of both KIM-1 and NGAL suggest that tubule damage may have started in these patients before the development of high creatinine levels and/or renal failure. This also points out potential utility of markers such as NGAL and KIM-1 for early recognition of kidney damage.

Limitations

There were few limitations in our study. First one is the small sample size and its single-center design. Second, neither KIM 1 nor NGAL levels were detected before diagnosis of FMF. Second is that urinary, but not tissue, levels of KIM 1 and NGAL levels were measured for confirmation. Third limitation is lack of longitudinal follow-up to examine temporal changes in the levels of these biomarkers.

Conclusion

In conclusion, urinary KIM-1 and NGAL expressions were demonstrated to be significantly increased in pediatric FMF patients. While findings indicating acute tubular damage such as proteinuria and hematuria have not developed, high urinary levels of these molecules may show that these can be used as early, reliable markers of kidney damage. It is thought that KIM-1 and NGAL may help early recognition of renal damage, early organization of treatment and evaluation of course of the disease in pediatric FMF patients. Larger multicenter clinical studies are needed to determine whether urinary KIM-1 and NGAL levels can be used routinely in the diagnosis and follow-up of FMF-related nephropathy. Examination of urinary KIM-1 and NGAL levels in patients with biopsy-confirmed acute tubular injury would improve their reliability in identifying of renal damage. Although routine use is not currently recommended, our individual demonstrated the necessity of multicenter longitudinal studies evaluating KIM-1 and NGAL in pediatric FMF nephropathy.

Conflict of interest: The authors have no conflict of interest to disclose.

Author Contributions		**Author Initials**
SCD	Study Conception and Design	AA, AY, ET
AD	Acquisition of Data	AA, AY, BSK, ET
AID	Analysis and Interpretation of Data	AA, ET, AME, CT, BSK,
DM	Drafting of Manuscript	AA, AY, CT, AME, BSK
CR	Critical Revision	AA, AY, CT, AME

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