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Original Article

Can High Mobility Group Box 1 Protein Predict Ongoing Subclinical Inflammation in Patients With Familial Mediterranean Fever?

High Mobility Group Box 1 Proteini, Ailevi Akdeniz Ateşi Hastalarında Süregelen Subklinik Enflamasyonu Öngerebilir mi?

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is an autoinflammatory disease that commonly presents with fever, peritonitis, and pleuritis. Recent studies have reported ongoing inflammation in the attack-free period of patients with FMF. High mobility group box protein (HMGB1) is a frequently investigated marker with a strong diagnostic and prognostic role for several chronic inflammatory diseases. The objective of this study was to evaluate the role of HMGB1 in patients with FMF.

Method: This cross-sectional study included a total of 57 (25 female/32 male) consecutive patients with FMF and a control group of 60 (30 female/30 male) healthy children. Demographic and clinical data of the patients were recorded. Blood samples were obtained from participants for HMGB1 analysis.

Results: The median age of the patients was 123 months. The median follow-up time of patients was 5 years. There was no statistically significant difference between the patient and control groups in terms of age, sex, and body weight. The most frequent *MEFV* gene mutation was M694V (78%). HMGB1 was higher in the patient group than in the control group (p=0.001). The levels of HMGB1 were not different between the attack and the attack-free period (p>0.05).

Conclusion: HMGB1 is significantly higher in FMF patients independent from being in the attack period. HMGB1 may demonstrate the ongoing subclinical inflammation in patients with FMF.

Keywords: DAMPs, HMGB1, FMF, subclinical inflammation, FMF attack-free period

ÖZ

Amaç: Ailevi Akdeniz ateşi (AAA) ateş, peritonit ve plevrit ile ortaya çıkan otoenflamatuvar bir hastalıktır. Yakın zamanlı çalışmalarda AAA hastalarında atak dışı dönemde de devam eden enflamasyon gösterilmiştir. High mobility group box 1 proteini (HMGB1) güçlü bir tanısal ve prognostik belirteç olarak çok sayıda kronik enflamatuvar hastalıkta araştırılmış bir proteindir. Çalışmanın amacı AAA hastalarında HMGB1'in rolünü araştırmaktır.

Yöntem: Bu kesitsel çalışmada toplam 57 (25 kız/32 erkek) AAA hastası ile 60 (30 kız/30 erkek) sağlıklı çocuktan oluşan kontrol grubu bulunmaktadır. Hastaların demografik ve klinik verileri kaydedilmiştir. Tüm hastalardan HMGB1 analizi için kan örneği toplanmıştır.

Bulgular: Hastaların medyan yaşı 123 aydı. Medyan takip süresi 5 yıldı. Hastalar ve kontrol grubu arasında yaş, cinsiyet ve vücut ağırlığı açısından anlamlı fark yoktu. Hastalardaki en sık *MEFV* gen mutasyonu M694V (%78) idi. HMGB1 hastalarda kontrol grubuna göre anlamlı olarak yüksekti (p=0,001). HMGB1 düzeyi atak ve atak dışı dönemdeki hastalarda benzerdi (p>0,05).

Sonuç: HMGB1, AAA hastalardında atak döneminden bağımsız olarak yüksektir. AAA hastalarında süregelen subklinik enflamasyonun bir belirteci olabilir.

Anahtar kelimeler: DAMPs, HMGB1, AAA, subklinik enflamasyonu, AAA atak dışı dönem

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive genetic disease that commonly affects the population living in the Mediterranean region[1]. The disease is characterized by repetitive self-limiting attacks of aseptic peritonitis, pleuritis, arthritis, and fever lasting for 1 to 3 days. The disease can be diagnosed with molecular genetic testing, which can identify the characteristic *MEFV* gene mutations. In the literature, many studies demonstrated that; interleukin-6 (IL-6), IL-12, IL-17, IL-18, INF-g, TNF-α, neutrophil-to-lymphocyte ratio (NLR), and red boold cell distribution width (RDW) were related to subclinical inflammation in the attack-free period[2,3]. These results support that there is ongoing inflammation in FMF patients even in the asymptomatic period of the disease[4,5]. The most devastating complication of FMF is amyloidosis, which can also develop in asymptomatic patients with subclinical inflammation[6,7]. There is no biological marker that has been reported to determine the severity of the ongoing subclinical inflammation that may predict the prognosis of the disease.

Damage-associated molecular pattern (DAMP) molecules have a role in physiological functions in the daily cycle of a cell and when they reach the extracellular environment, they have a major role in the signaling pathway of the tissue damage response[8]. High mobility group box 1 protein (HMGB1), a nuclear DNA binding protein, is one of these DAMPs[9]. HMGB1 is found in all human cells. To act like DAMPs, it should be released from the cell. It can passively be released from necrotic/apoptotic cells, and actively secreted from cells under stress such as monocytes, macrophages, and dendritic cells. HMGB1 enhances the immune response and induces the release of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 via RAGE, TLR2, and TLR4[10-12].

The inhibiting role over apoptosis-associated speck-like protein (ASC) with a caspase activation and recruitment domain (CARD) is disappeared with pyrine mutation. As a result, the release of caspase 1 leads to elevated IL-1 and NF-κB activation. The cell then proceeds to apoptosis/proptosis and triggers inflammation. HMGB1 is released actively in proptosis. This circumstance may present a different perspective on the ongoing pyrine deficiency in the attack-free period of the disease and the subclinical inflammation mechanism. The relationship between HMGB1 and autoimmune diseases such as systemic lupus, rheumatoid arthritis, and inflammatory myositis has been reported previously[11,13,14]. An elevation in HMGB1 may be seen in serum, synovial fluid, and the extracellular matrix of skin lesions in several diseases[11,13,15].

There are a few studies in the recent literature that demonstrate the subclinical inflammation in FMF patients in the attack-free period. This study aimed to determine whether the pro-inflammatory cytokine HMGB1 can be used as an indicator of inflammation in FMF patients with or without attack.

MATERIALS and METHODS

This cross-sectional study was conducted in the Pediatric Nephrology Department and was approved by the ethical board of the Başkent University (project no: KA15/350, date: 23.12.2015). The study was performed between January 2016 and November 2016. All patients and their parents signed an informed consent form before they were included in the study.

Study Population

Sixty consecutive patients with a diagnosis of FMF with or without attack were included in the study. All patients met the diagnostic criteria of Tel Hashomer[16] and Yalçinkaya[17] for FMF and all their genetic studies had been previously completed. The patients had no other concomitant diseases. Three patients were excluded due to the lack of genetic mutation analysis records, and therefore, 57 patients were analyzed in the study group. A control group was formed of 60 healthy age and sex-matched subjects selected from patients presenting for routine screening, with no known disorders, and volunteered for participation in the study with the approval of their legal guardians. The study group was aged between 5 and 18 years. Data were retrieved from the hospital records. The date of diagnosis, genetic mutation analysis, treatments of the patients, the duration of treatment, family history of the patients, and consanguineous marriage was recorded. Patients were excluded if they had any coexisting chronic disease such as amyloidosis or renal failure, or if they were not treated with colchicine.

Blood Sample Collection and Analysis

1 mL of venous blood sample was obtained for HMGB1 analysis from all participants. The blood samples were analyzed with an enzyme-linked immunosorbent assay kit for high mobility group protein 1 (HMG1) (Cloud-Clone Corp® Houston, TX, USA). This assay kit is sensitive for 12.5-800 pg/mL of HMGB1 level. The

test was performed by a laboratory assistant blinded to the groups. The blood samples of the patients were also analyzed for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count, fibrinogen, creatine kinase, aspartate aminotransferase, alanine aminotransferase, and blood creatinine. Urine samples were analyzed for microalbumin.

Statistical Analysis

The main outcome was the level of serum HMGB1 in patients and power analysis was used to adjust the sample size before the beginning of the study to compare the FMF patients and control group regarding recent literature. The sample size was calculated as requiring at least 49 subjects in each group for a power of 0.80 and α=0.05. Data obtained in the study were analyzed statistically using SPSS ver. 20.0 for Windows (IBM SPSS Inc., NY, USA). The Shapiro-Wilk test was used to assess the normal distribution of the data. Quantitative variables were expressed as median and minimum-maximum values and qualitative variables as frequencies. In the comparisons between groups, normally distributed variables were compared with the Student's t-test and non-normally distributed variables with the Mann-Whitney U test. Categorical variables were compared with the chi-square test. Spearman rank correlation coefficient was employed to determine the correlation between HMGB1 and other variables. A value of p<0.05 was considered statistically significant.

RESULTS

The median age of patients was 123 months (minimum: 20 - maximum: 220) and while 55 (47%) of them were boys, 62 (53%) were girls. There was no significant difference in age, sex, or body weight between the patients and the healthy control group (Table 1). The median follow-up duration was 5 years (range, 1 to 12 years) and the median age at disease onset was 5 years (range, 0 to 13 years). Five patients were in the attack period and 52 patients were in the attack-free period. Positive family history was determined in 33 (57.9%) patients with FMF, and 6 (10.5%) patients had consanguineous parents. M694V gene mutation was present in 45 (78.7%) patients with at least one allele and 19 patients had homozygous M694V mutations, one patient had homozygous M608I mutations. All patients with FMF were under colchicine treatment at a median dose of 1 mg/day (0.5-1.5 mg/day).

The median HMGB1 level was higher in patients with FMF [47.9 ng/dL (21-406)] compared to healthy control subjects [32.7 ng/dL (16-118)] (p<0.001). In FMF group, the median level of HMGB1 was 47.9 ng/dL (21-321) in girls (n=25) and 49.9 ng/dL (29-405) in boys (n=32) (p=0.303). Serum HMGB1 levels were not statistically different between patients with a ≥5 years follow-up duration of and <5 years follow-up duration [49.5 ng/dL (21-406) vs 46.7 ng/dL (23-321), respectively, p=0.533]. The levels of HMGB1 showed no difference between patients with and without a family history (p=0.566), and with and without parental consanguineous marriage (p=0.621). There was no association between serum HMGB1 levels and gene mutations. Serum HMGB1 levels were not correlated with CRP, ESR, blood cell counts, liver enzymes, fibrinogen, and urine microalbumin levels. Also, no correlation was found between the duration of follow-up and HMGB1 levels (Table 2).

However, the median hemoglobin, platelet, ESR, CRP, fibrinogen, RDW levels, and neutrophil/lymphocyte ratio were significantly different between patients with and without attack, and the levels of serum HMGB1 were not higher in patients with the attack (Table 3).

DISCUSSION

Due to the disappearance of inhibiting effect of pyrin on ASC through mutation in the MEFV gene and over-production of caspase 1, cell apoptosis/proptosis may be aggravated in patients with FMF. HMGB1 is actively released during this proptosis process[18,19]. After the release of HMGB1 from the necrotic tissues, it acts as a DAMPs molecule and induces dendritic cell maturation and migration, and controls the activation of T cells through RAGE. Thus, it acts as an important mediator of sterile inflammation as a part of native immunity[20]. These cells produce pro-inflammatory signals and cytokines

Table 1. Demographical characteristics and main laboratory findings of the groups

	FMF (n=57)	Healthy controls (n=60)	p-value
Age, months*	123 (20-220)	122.5 (22-216)	0.866
Gender, n (female/male)	25/32	30/30	0.580
Body weight, kg*	33.9 (12.5-116)	37 (14-98)	0.594
HMGB1 (ng/dL)	47.9 (21-406)	32.7 (16-118)	0.001

FMF: Familial Mediterranean fever, HMGB1: High mobility group box 1 protein. *Values given as median (minimum-maximum)

and aggravate inflammation. Recent studies related to the pro-inflammatory cytokine activity of HMGB1 have demonstrated the role of HMGB1 as a dangerous signal in autoimmune diseases such as rheumatoid arthritis, and systemic lupus erythematosus[11,21]. The most important finding of the current study was the levels of HMGB1 did not differ in attack or attack-free periods. To the best of our knowledge, no study in recent literature has evaluated HMGB1 levels in patients with FMF. The results of this study showed that HMGB1 was elevated regardless of the attack or remission period of FMF. NLR, platelet to lymphocyte ratio, MPV, and RDW have previously been reported to be elevated in patients with FMF in the attack-free period[2]. MPV, splenomegaly, and NLR have been reported as indicators of ongoing inflammation in patients with FMF[22,23]. In addition to elevated HMGB1 in the attack-free period, HMGB1 was also correlated with NLR and RDW in the current study. These parameters

Table 2. The demographic and laboratory variables in FMF patients and their correlation with HMGB1

Variable	Median	Correlation coefficient	p-value
Age (months)	126 (22-216)	-0.012	0.897
Body weight (kg)	33.9 (12.5-116)	-0.042	0.656
Creatinine (mg/dL)	0.58 (0.4-0.88)	-0.035	0.798
CRP (mg/L)	2.63 (0.2-77.8)	-0.074	0.585
ESR (mm/h)	7 (2-66)	-0.019	0.891
White blood cell (k/µL)	7660 (3970-13930)	0.059	0.664
Fibrinogene (mg/dL)	306 (192-602)	-0.144	0.287
Colchicine dose (mg/day)	1 (0-1.5)	0.175	0.192
Follow-up time, years	5 (1-12)	0.020	0.882
Urine microalbumine (mg/gr/cre)	9.2 (3-34.9)	-0.022	0.871
MPV (fL)	7.33 (5.3-10.7)	0.112	0.447
Neutrophyl/lymphocite	1.22 (0.4-4.3)	R=0.350	0.02
RDW (%)	13.35 (10.6-17.4)	R=0.285	0.04

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: mean platelets volume, RDW: Red blood cell distribution width, FMF: Familial Mediterranean fever, HMGB1: High mobility group box 1 protein

Table 3. The laboratory findings in patients with and without FMF attack

	Patients in attack period (n=5)	Patients in attack-free period (n=52)	p-value
HMGB1 (ng/dL)	42.2 (35-100)	48.3 (21-406)	0.774
CRP (mg/L)	51 (36.5-77.8)	1.8 (0.2-65)	<0.001
Fibrinogene (mg/dL)	452 (412-551)	295 (192-602)	<0.001
Erythrocyte sedimentation rate (mm/h)	30 (9-66)	6.5 (2-31)	0.001
Hemoglobine (g/dL)	12.3 (10.6-13)	13.1 (10.2-16)	0.035
White blood cells (k/µL)	8290 (4670-11600)	7485 (3970-13930)	0.356
Platelets (k/µL)	387000 (214000-495000)	295000 (157000-478000)	0.048
Creatinin (mg/dL)	0.55 (0.51-0.61)	0.59 (0.4-0.88)	0.206
AST (U/L)	20 (16-29)	22 (13-35)	0.651
ALT (U/L)	15 (7-23)	17 (9-49)	0.250
CK (U/L)	92 (37-127)	100 (32-280)	0.519
Urine microalbumine (mg/gr/cre)	7.2 (4.2-9.9)	9.2 (3-34.9)	0.262
Neutrophyl/lymphocite	1.85 (0.7-4.1)	1.18 (0.4-4.3)	0.04
RDW (%)	15.5 (14.4-16.2)	13 (10.6-17.4)	0.04
MPV (fL)	7.2 (5.7-8.4)	7.33 (5.3-10.7)	0.482

HMGB1: High mobility group box 1 protein, CRP: C-reactive protein, AST: Alanin aminotransferaz, ALT: Aspartate aminotransferaz, RDW: Red blood cell distribution width, MPV: Mean platelets volume , FMF: Familial Mediterranean fever, CK: Creatine kinase

may indicate subclinical inflammation in patients with FMF.

As an indicator of ongoing inflammation, the elevated HMGB1 in the attack-free period in patients under colchicine treatment may indicate insufficient control of the subclinical inflammation. Although colchicine treatment is known to reduce attack frequency and serious complications such as amyloidosis, to date, the clinical outcomes of the subclinical inflammation despite colchicine treatment are not known[24]. Gunes et al.[25] reported that kidney damage in patients with FMF is due to ongoing minimal inflammation and that urinary microalbumin can be used as a marker of kidney damage. The urine microalbumin and HMGB1 were not found to be correlated in the current study. This may be related to the short disease duration time of the patients[26]. Therefore, considering the limited exposure of patients to ongoing subclinical inflammation and the absence of pathologic microalbuminuria may have concealed the predictive value of HMGB1 for amyloidosis in this study. Long-term outcomes of these patients may give an idea about the predictive value of HMGB1 for amyloidosis.

The most common mutations in FMF patients are M694V, V726A, M680I, and M694I[27,28]. The mutations in the current study were compared with the literature and 78% of patients had M694V mutation in at least one allele. Prasad et al.[29] reported that patients with M694V mutation had earlier disease onset, had less response to colchicine, and more frequently developed amyloidosis. However, no significant relationship between M694V mutation and poor prognosis of the disease has been demonstrated[30]. Similarly, no significant HMGB1 difference was observed between the patients with and without M694V mutation in this study. As the relationship between the type of mutation and the prognosis is considered, it may be concluded that HMGB1 may not predict prognosis in these patients. There is a need for further studies with more patients and longer follow-ups to clarify the relationship between HMGB1 and the prognosis of the disease and the risk for amyloidosis.

As expected, the acute inflammation markers were higher in patients in the FMF attack period but HMGB1 was similar to that of patients in the attack-free period in the current study. HMGB1 has been reported to be elevated in later periods of inflammation[31]. However, HMGB1 was elevated in all patients in the current study, whether in the attack or attack-free period, so it can be concluded that HMGB1 is elevated in patients with FMF regardless of whether they are in attack or attack-free period. It can also be speculated that HMGB1 in patients with FMF probably projects the long-term inflammation of the patients which may indicate the effective control of the disease with colchicine treatment.

Study Limitations

However, the limited number of patients in the attack period was a major limitation of this study, and studies with a higher number of patients in the attack period of the disease are needed to draw definitive conclusions about the differences in HMGB1. In addition, the lack of control groups including various types of autoinflammatory diseases limits the study to rule out the specificity of HMGB1 in patients with FMF.

CONCLUSION

The results of this study demonstrated that serum HMGB1, which indicates cellular stress and ongoing subclinical inflammation, is elevated in patients with FMF when compared to healthy controls. In addition, the elevated HMGB1 in patients with FMF is not associated with the attack period of the disease.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted in the Pediatric Nephrology Department and was approved by the ethical board of the Başkent University (project no: KA15/350, date: 23.12.2015).

Informed Consent: All patients and their parents signed an informed consent form before they were included in the study.

Authorship Contributions

Surgical and Medical Practices: B.Ö., Concept: K.G., B.A., N.B., F.İ.Ş., Design: B.Ö., E.B., Data Collection or Processing: B.Ö., N.B., F.İ.Ş., Analysis or Interpretation: N.B., Literature Search: B.Ö., Writing: B.Ö., F.İ.Ş.

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

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