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Original Article

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The Association of Serum Prolidase Enzyme Activity with the Presence of Familial Mediterranean Fever

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Abstract

Objective: Uncontrolled inflammation and oxidative stress are responsible for the pathogenesis of familial Mediterranean fever (FMF) and its complications. Increased serum prolidase enzyme activity (SPEA) has been shown to correlate with inflammation and oxidative stress. This study aimed to evaluate the relationship between SPEA and FMF disease.

Materials and Methods: A total of 124 participants were included in this cross-sectional study. Patients were divided into two groups depending on the presence or absence of FMF attacks. Group 1 consisted 69 patients who were attack free. Group 2 consisted of 11 patients who suffered FMF attacks. A total of 44 healthy volunteers were included in the study (Group 3). Clinical features and laboratory data were recorded. SPEA was analyzed by using spectrophotometry.

Results: SPEA of Group 2 was found to be statistically significantly higher than that of Groups 1 and 3 (p=0.004 and p=0.006, respectively). SPEA was positively correlated with the presence of attack (r_s=0.265, p=0.003), erythrocyte sedimentation rate (r_s=0.269, p=0.003), and C-reactive protein (r_s=0.199, p=0.027). The relationship between FMF attack and SPEA was evaluated by receiver operating characteristics analysis. Sensitivity and specificity were 91% and 67%, respectively, with an SPEA cut-off point of 817 U/L (AUC=0.769 [95% CI 0.626-0.912, p=0.003]).

Conclusion: The FMF attack and the associated acute phase response may have an effect on increased SPEA. In FMF patients, an increased SPEA may play a role in both pathogenesis and progression of complications caused by the inflammatory process.

Keywords: Familial Mediterranean fever, inflammation, prolidase

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease affecting mostly the ethnic groups of eastern Mediterranean origin. It has typical characteristic features of self-limiting recurrent inflammatory attacks with fever, polyserositis, and increased acute phase reactants (1). The mutation in the MEFV gene on the 16th chromosome that encodes the pyrin protein is responsible for the pathogenesis of the disease. The mutation in pyrin causes an insufficient control of the inflammatory process (2) and results in oxidative stress, which leads to molecular damage of cells due to overproduction of free radical and reactive oxygen species (3). It has been shown that inflammation in FMF disease, with or without an attack, is effective in the formation of oxidative stress (4, 5).

Prolidase, a member of the matrix metalloproteinase family, is a cytosolic exopeptidase that specifically cleaves imidodipeptides containing proline and hydroxyproline at the C-terminal. This enzyme plays an important role in collagen metabolism, matrix remodeling, and cell growth (6). In addition to plasma, it has been detected in leucocytes, erythrocytes, and fibroblasts (7). It has also been shown to play a role in physiological and pathological processes associated with inflamma-

tion, such as wound healing and cell migration (8). It has been stated that an increase in the serum prolidase enzyme activity (SPEA) is associated with oxidative stress and may play a role in the pathogenesis of some diseases through the collagen cycle disruption (9-10). However, the effect of the SPEA change on the pathophysiological mechanisms of the diseases has not been clear yet.

Factors affecting inflammation in FMF patients are currently under investigation. To the best of our knowledge, the role of SPEA in FMF disease, and its complications are still unknown. We investigated the relationship between SPEA and disease activity in patients with FMF, since we consider that variability in SPEA may have an effect on pathophysiological mechanisms.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional study was conducted between February 2018 and March 2019 in nephrology and rheumatology clinics and included a total of 124 participants. The study was approved by the Hitit University School of Medicine Ethics Committee in accordance with the Helsinki 2018 declaration (Approval Date: January 16, 2018; Approval Number: 2018-09), and all participants were informed about the study and their written informed consent was obtained.

A total of 80 FMF patients diagnosed according to the Tel-Hashomer criteria (11) were included in the study. The patients were divided into two groups as FMF-attack-free period [(FMF-AFP), Group 1 (n=69) (29 men, 40 women; mean age 32.7±10.8 years; ages ranging between 18 and 63 years)] if the patient did not suffer from any attacks in the last month, and FMF-attack period [(FMF-AP), Group 2 (n=11) (4 men, 7 women; mean age 33.0±13.2 years; ages ranging between 19 and 48 years)] if there was an attack at the time of study inclusion. The control group consisted of 44 matched healthy volunteers (Group 3, 22 men, 22 women; mean age 31.1±7.6 years; ranging between 19 and 46 years) with normal physical examination and laboratory findings and no history of chronic disease. Demographic and somatometric data of the participants were determined. Disease diagnosis time, colchicine dose, and regular use were questioned. Compliance with treatment was recorded.

Main Points

- In this study, SPEA was significantly higher in the FMF-attack period group than in the FMF-attack-free period group and in healthy controls.
- However, positive correlations between SPEA and both FMF activation and some inflammatory markers were shown.
- The FMF attack and the associated acute phase response may have an effect on increased SPEA.
- Increased SPEA may play a role in both pathogenesis and complications caused by the inflammatory process in FMF patients. Therefore, monitoring of SPEA can be used in early and more accurate detection of complications, especially in patients with frequent attacks.

Patients with acute or chronic infectious disease, endocrine disease (thyroid, parathyroid, diabetes mellitus), hypertension, hyperlipidemia, acute or chronic organ failure (heart, kidney, liver, lung), malignancy, surgical intervention in the last month, other autoimmune or inflammatory diseases, those using agents that may affect SPEA (antioxidants, non-steroid anti-inflammatory drugs, renin-angiotensin-aldesterone system blockers, and statin) and smokers were excluded from the study.

Fasting blood samples with 8 to 10 hours of fasting were taken for blood urea nitrogen, creatinine, glucose, alanine aminotransferase, high density lipoprotein cholesterol, low density lipoprotein cholesterol, fibrinogen, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count analysis from all participants. These blood samples were taken from FMF-AP group 24 hours after the onset of the attack. In addition, first urine sample was taken in the morning to assess the protein excretion. Blood samples for SPEA assay were centrifuged at 3,000 rpm for 10 minutes to get serum and then stored at -80°C until the day of analysis.

Biochemical parameters were measured with Beckman Coulter AU 5800, and complete blood count was performed with Mindray BC-6800 hematology analyzer. Estimated glomerular filtration rate values were determined using the chronic kidney disease epidemiology collaboration equation (12). Serum CRP and ESR levels were measured by nephelometric and Westergren methods, respectively. Protein excretion was calculated using the spot urine protein/creatinine ratio.

Measurement of Serum Prolidase Enzyme Activity

To measure the serum prolidase enzyme activity, 25 µL of serum sample was added to the 75 µL of activation solution (50 mmol/L TrisHCl buffer at pH 7 containing 1 mmol/L GSH, 50 mmol/L$MnCl_2$) and incubated at 37°C for 30 minutes. Then, 100 µL of 144 mmol/L Gly-Pro was added into the mixture and was incubated at 37°C for 5 minutes. After incubation, 1 mL of glacial acetic acid was added to stop the reaction. Next, 300 µL of TrisHCl buffer (pH 7.8) and 1 mL of ninhydrin solution (3 g/dL ninhydrin was dissolved in 0.5 M of orthophosphoric acid) were added into the mixture, and then incubated at 90°C for 25 minutes. All samples were chilled with ice and read at 515 nm against the reagent blank without delay using a spectrophotometer (Biochrom Ltd.; Cambridge CB4 OFJ England, Libra S60). SPEA was defined as proline in µmol/L that formed in 1 minute. Within day and between day % coefficients of variation of the method were found to be below 10% for high and low serum values (13).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences SPSS 23.0 package for Win-

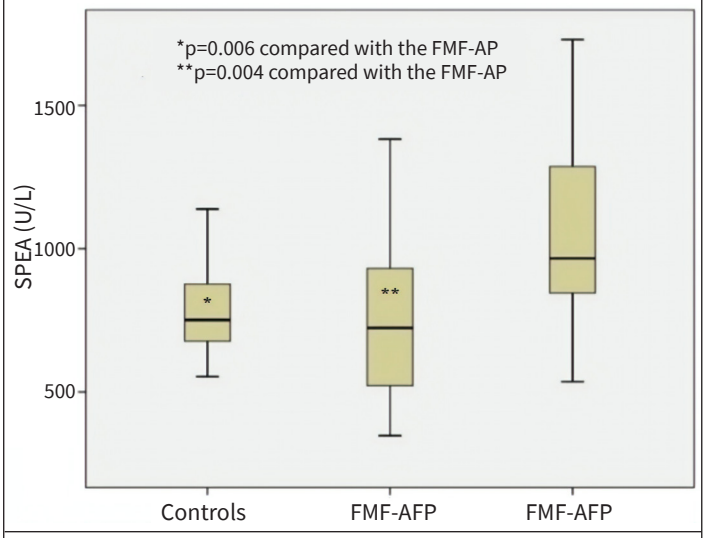

Figure 1. Comparison of serum prolidase enzyme activity (SPEA) between groups
FMF-AFP: familial Mediterranean fever-attack-free period; FMF-AP: familial Mediterranean fever-attack period

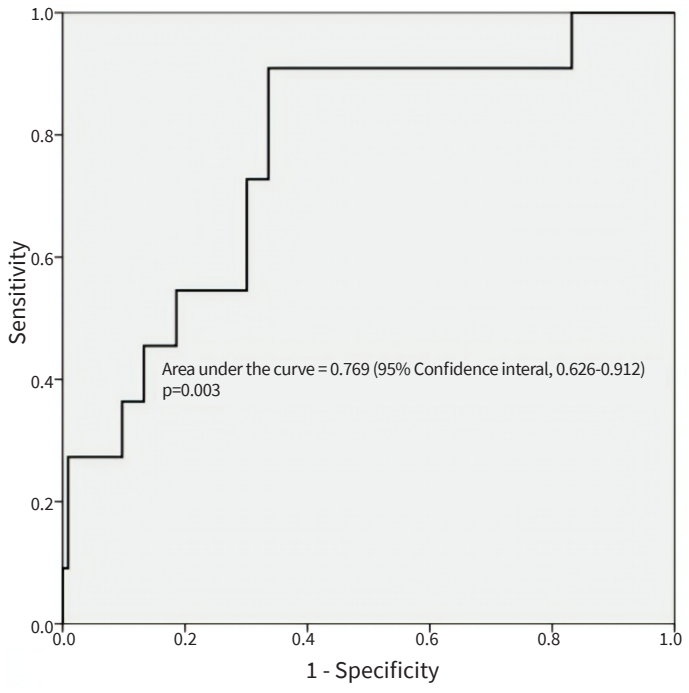

Figure 2. Evaluation of relationship between SPEA value and FMF attack by receiver operating characteristic (ROC) analysis

dows (IBM Corp.; Armonk, NY, USA). Demographic and biochemical features were classified as continuous or categorical variables, as appropriate. Kolmogorov Smirnov analysis was used to test the normality. Data were expressed as mean±standard deviation and median (25^{th}-75^{th} quartile) for Gaussian and non-Gaussian distributed variables, respectively. Comparisons among groups were done using the one-way ANOVA and Kruskall Wallis variance analyses, and then Bonferroni correction was done, as appropriate. Categorical variables were compared using the chi-square test. Spearman's rank correlation coefficient was used to identify the associations between SPEA and evaluated variables. The relationship between SPEA values and FMF attack was evaluated by receiver operating characteristic (ROC) analysis. All reported p-values were two tailed, and those less than 0.05 were considered to be statistically significant.

RESULTS

There was no statistically significant difference between the groups in terms of age, gender, and body mass index. There was also no statistically significant difference in disease duration and colchicine doses (p>0.05), but the compliance with colchicine was insufficient in Group 2 (p<0.001) (Table 1).

SPEA levels of Group 2 was significantly higher than the other two groups (p=0.007). In the comparison between the groups, SPEA levels of Group 2 were significantly higher than those of Groups 1 and 3 (p=0.004 and p=0.006, respectively) (Figure 1). It was seen that urinary protein excretion was significantly higher in Group 2 than Group 3 (p=0.005). The comparison of other laboratory values between the groups is detailed in Table 1.

In the correlation analysis, SPEA was positively correlated with the presence of FMF attack (r_s=0.265, p=0.003), ESR (r_s=0.269, p=0.003), and CRP (r_s=0.199, p=0.027) (Table 2).

The relationship between FMF attack and SPEA values was evaluated by ROC analysis in all participants. The cut-off value of the SPEA was 817 U/L, with a sensitivity of 91% and specificity of 67% (area under the curve=0.769 [95% confidence interval 0.626-0.912, p=0.003]) (Figure 2).

DISCUSSION

In this study, SPEA was significantly higher in the FMF-AP group than in the FMF-AFP group and healthy controls, but no statistically significant difference was found between FMF-AFP group and controls. SPEA was also positively correlated with disease activity and inflammation.

The main pathological mechanism in FMF is uncontrolled inflammation due to the mutation in pyrin protein that is mostly found in neutrophils and macrophages that plays an important role in apoptosis and inflammation. In these patients, interleukin-1β (IL-1β) released from uncontrolled neutrophils and macrophages has been shown to exacerbate the inflammatory response (14). It is a known fact that blood neutrophil count increases and neutrophils flow to the inflammation area in FMF attack (15). In our study, ESR, CRP, NLR, and monocyte counts, which are among the inflammatory biomarkers, showed a positive correlation with FMF disease activity.

A positive relationship between acute phase reactants and oxidative stress markers has been shown in FMF patients (4, 5). The relationship between increased SPEA and oxidative stress has been demonstrated in several studies (11, 13). In addition, it

Table 1. Demographic and biochemical data of participants

Parameters	Group 1 (n=69)	Group 2 (n=11)	Group 3(n=44)	p
Age, years	34 (24-40)	30 (24-48)	29 (25-38)	0.948
Male, n (%)	29 (42%)	4 (58.1%)	22 (50)	0.631
BMI, kg/m^2	24.6±4.6	22.4±3.2	24.3±3.8	0.278
Duration of disease, years	14 (7-20)	8 (3-18)	-	0.126
Colchicine, mg/day	1.5 (1.0-1.5)	1(0.5-1.5)	-	0.792
Treatment compliance, n (%)	62 (89.9)	4 (36.4)	-	<0.001
Hemoglobin, g/dL	14.1±1.7	13.6±1.5	14.4±1.2	0.176
RDW, %	13.5 (12.9-14.3)[a]	13.4 (12.9-14.3)	13.1 (12.7-13.4)	0.032
Leukocyte, ×10^9/L	6.7 (5.7-7.7)[b]	7.5 (6.6-12.85)[c]	6.3 (5.5-7.5)	0.068
NLR	1.8 (1.5-2.4)	2.4 (2.2-4.7)[d, e]	1.9 (1.4-2.4)	0.028
Monocytes, ×10^9/L	0.44±0.12	0.65±0.27[f, g]	0.50±0.15	<0.001
Glucose, mg/dL	89 (82-95)	88 (81-101)	89 (86-94)	0.732
BUN, mg/dL	3.7±0.5	3.6±0.4	3.6±0.4	0.301
Creatinine, mg/dL	0.7 (0.55-0.8)	0.6 (0.6-0.8)	0.7 (0.6-0.8)	0.546
eGFR (mL/min/1.73 m^2)	119±16	120±11	121±11	0.749
ALT, U/L	21 (13-35)	19 (10-25)	16 (12-26)	0.122
HDL-C, mg/dL	47±11	44±9	49±12	0.295
LDL-C, mg/dL	102±36	89±39	102±34	0.548
ESR, mm/hour	11 (5.5-18.5)[h]	29 (22-58)[i, j]	6.3 (5-10)	<0.001
CRP, mg/L	3 (3-5.3)[k]	23 (11-74)[l, m]	3.1 (3-3.1)	<0.001
Fibrinogen, mg/dL	271±51	435±103[n, o]	283±59	<0.001
UPE, mg/day	75 (60-96)	129 (61-204)[p]	68 (55-84)	0.066
Prolidase, U/L	723 (517-935)	966 (825-1,466)[q, r]	751 (676-880)	0.007

Categorical data are presented as frequencies and percentages; continuous variables are presented as mean±standard deviation or median (25th-75th quartile) depending on their distributions
[a]p=0.009 compared with the Group 3
[b]p=0.036 compared with the Group 3
[c]p=0.024 compared with the Group 3
[d]p=0.01 compared with the Group 3
[e]p=0.009 compared with the Group 1
[f]p=0.036 compared with the Group 3
[g]p=0.001 compared with the Group 1
[h]p=0.005 compared with the Group 3
[i]p<0.001 compared with the Group 3
[j]p<0.001 compared with the Group 1
[k]p=0.047 compared with the Group 3
[l]p<0.001 compared with the Group 3
[m]p<0.001 compared with the Group 1
[n]p<0.001 compared with the Group 3
[o]p<0.001 compared with the Group 1
[p]p=0.005 compared with the Group 3
[q]p=0.006 compared with the Group 3
[r]p=0.004 compared with the Group 1
ALT: alanine aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FMF: familial Mediterranean fever; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; RDW: red blood cell distribution width; NLR: neutrophil to lymphocyte ratio; UPE: urinary protein excretion

was emphasized that changes in prolidase enzyme activity may be associated with tissue damage in many diseases in which inflammation is effective in the pathogenesis (16). Recently, in a study involving patients with FMF-AFP, SPEA was found higher than the control group (17). In our study, SPEA of patients with FMF-AFP were not different from those of the controls. This may be due to the difference in study populations and SPEA identification methods. However, positive correlations between SPEA

Table 2. Correlation analysis of variables with serum prolidase enzyme activity

	Serum prolidase enzyme activity (n=124)	
Variables	**r_s**	**p**
Age	0.047	0.605
Gender	-0.086	0.343
BMI	-0.055	0.544
Duration of disease	-0.044	0.697
Presence of attack	0.265	0.003
Hemoglobin	-0.105	0.262
RDW	0.076	0.420
Leukocyte	-0.017	0.848
NLR	-0.146	0.119
Monocytes	0.030	0.751
Glucose	0.070	0.443
eGFR	0.003	0.974
HDL-C	0.032	0.721
LDL-C	0.097	0.288
UPE	0.104	0.259
ESR	0.269	0.003
CRP	0.199	0.027
Fibrinogen	0.121	0.181

Significance was determined with the Spearman rank correlation coefficient
BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; RDW: red blood cell distribution width; NLR: neutrophil to lymphocyte ratio; UPE: urinary protein excretion

and both FMF activation and some inflammatory markers were shown. Similar to previous studies, these data support the association of increased inflammation with FMF activity. The FMF attack and the associated acute phase response may have an effect on increased SPEA.

There are insufficient studies on the importance of SPEA and the factors affecting its activity in the FMF pathogenesis. The nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing-3 (NALP3) inflammasome is known to be effective in the inflammatory response (18). Also, regulation of NALP3 inflammasome has a central role in the pathogenesis of FMF. Pyrin negatively affects NALP3 inflammasome activation, and suppresses the formation of caspase-1, necessary for IL-1β synthesis, from pro-caspase-1 (19). In the study conducted by Campbell et al. (20), a positive correlation between prolidase enzyme activity and NALP3 inflammasome expression was demonstrated in synovial membrane samples of patients with chronic osteoarthritis. The results of our study suggest that SPEA may affect inflammation through NALP3 inflammasome activation in the FMF pathogenesis.

Prolidase is a manganese-dependent matrix metalloproteinase, which plays a key role in collagen synthesis (8). Nitric oxide (NO), a signaling molecule, regulates many processes, including collagen synthesis and matrix remodeling. It has been shown that NO stimulates collagen synthesis and prolidase activity in fibroblasts. NO acts on this enzyme by increasing serine/threonine phosphorylation (21). There have been conflicting results in studies that evaluated oxidative stress, NO levels, and prolidase enzyme activity. It was shown that both NO levels and prolidase activity in bladder tissue samples were higher in patients with bladder tumors than in those without bladder tumors (22). In another study, it was emphasized that decreased SPEA and high NO levels may be associated in patients with diabetic neuropathy (23). In FMF patients, plasma NO levels were found to be lower during the attack period compared with the attack-free period (24). In a study in children with FMF, it was shown that plasma NO levels were higher in the attack-free period than healthy controls (25). In this patient group, we believe that the relationship between NO and SPEA may interact with the inflammation signaling pathway.

There are insufficient studies on the importance of SPEA and factors affecting its activity in the pathogenesis of renal injury. In a study evaluating the relationship between SPEA and proteinuria, increased SPEA was associated with microalbuminuria in patients with type 2 diabetes mellitus (26), whereas in another study, higher SPEA and oxidative stress were found in patients with diabetic nephropathy (27). Proteinuria influences the regulation of the signaling pathways of tubule cells, resulting in the production of pro-inflammatory factors that cause inflammation and fibrosis (28). In our study, although urinary protein excretion was higher in patients with FMF attack than in healthy volunteers, no correlation was found between urinary protein excretion and SPEA. We believe that this may be related to the absence of patients with overt proteinuria in the study population. Therefore, the role of prolidase enzyme activity in the pathogenesis of proteinuria-induced renal fibrosis should be investigated in the FMF patient population, which is included in those with proteinuria.

Colchicine is the basic drug to treat FMF. Regular use of this drug is important to prevent FMF attack, amyloidosis, and to suppress inflammation (29). However, the effect of colchicine on SPEA has been shown to be variable (30). Therefore, in our study, blood samples were collected before colchicine was used. We anticipate that increased inflammation leads to increased urinary protein excretion and high SPEA in the FMF-AP group with high treatment incompliance.

There are a number of limitations in the current study. First, the number of cases was relatively limited, and patients with amyloidosis were not included. Second, proline, hydroxyproline, and nitric oxide levels were not measured.

CONCLUSION

As a result, patients with FMF-AP had higher SPEA than those with FMF-AFP and healthy controls. There was a positive correlation between acute phase response and SPEA. Increased SPEA may play a role in both pathogenesis and progression of complications caused by inflammatory process in FMF patients. Therefore, monitoring of SPEA can be used in early and more accurate detection of complications, especially in patients with frequent attacks. Our findings should be supported by large-scale prospective studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hitit University School of Medicine (Approval Date: January 16, 2018; Approval Number: 2018-09).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.E.; Design - B.E.; Supervision - B.E.; Materials - N.Y., İ.A.; Data Collection and/or Processing - İ.D., B.E., İbrahim D.; Analysis and/or Interpretation - B.E., H.K.; Literature Search - B.E., H.K.; Writing - B.E., H.K.; Critical Reviews - B.E., H.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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