

The relationship between zinc status and inflammatory marker levels in FMF

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ABSTRACT

Aims: This study aimed to evaluate serum zinc concentrations in individuals diagnosed with FMF and to determine whether zinc status influences inflammatory activity.

Methods: We retrospectively reviewed the medical records of patients with FMF, who were under the follow-up of our nephrology-rheumatology center between 2018 and 2025.

Results: One hundred twelve FMF patients (M/F=52/60) with a mean age of 11.9 ± 5.1 years were included in this study. 35 (31.3%) of the patients have compound heterozygous mutation and 77 (68.8%) have heterozygous mutation. There was no difference in mean of leucocyte count and zinc level between these mutation groups. The mean pre-treatment sedimentation was significantly higher in patients with frequent attacks ($p=0.021$). However there was no difference between the attack frequency groups in mean of gender age, both of pre and post-treatment CRP, zinc, leucocyte count and post-treatment sedimentation ($p>0.05$). There was a positive correlation between mean zinc and mean leucocyte count, CRP levels ($p=0.019$, $r=0.334$ and $p=0.016$, $r=0.344$ respectively), but not with sedimentation.

Conclusion: Notably, in our current study, serum zinc levels were positively associated with inflammatory markers in FMF patients.

Keywords: Familial Mediterranean fever, zinc, inflammation, C-reactive protein, leukocyte count, pediatric rheumatology

INTRODUCTION

Chronic inflammation is known to contribute to progressive tissue and organ damage and is associated with a greater likelihood of developing chronic diseases. Inflammation is typically characterized by increased levels of acute-phase reactants such as C-reactive protein (CRP), leucocyte count, erythrocyte sedimentation rate (ESR) and other inflammatory mediators (IL-6, TNF- α).¹ Zinc, recognized for its antioxidant and anti-inflammatory functions, has been found to inversely correlate with CRP concentrations in previous studies.^{2,3} Zinc supports the activity of these antioxidant enzymes and serves as a key micronutrient in defending cells against oxidative stress.^{4,5} Familial Mediterranean fever (FMF) is a hereditary inflammatory disorder associated with mutations in the MEFV gene, located on chromosome 16p, which encodes the pyrin (also known as marenostrin) protein.⁶ Pyrin is predominantly expressed in neutrophils and regulates intracellular pathways that drive excessive IL-1 β production.⁷

This study aimed to evaluate serum zinc concentrations in individuals diagnosed with FMF and to determine whether zinc status influences inflammatory activity.

METHODS

The ethics committee approval of the study was obtained from the Kırıkkale University Clinical Researches Ethics Committee (Date: 25.06.2025, Decision No: 2025.25.08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients diagnosed with FMF during the study period were included in the study. We retrospectively reviewed the medical records of patients with FMF, who were under the follow-up of our nephrology-rheumatology center between 2018 and 2025. At the time of data entry we recorded demographic information, the data on mutation type, and

the levels of zinc, CRP, leucocyte count, and ESR at the pre-treatment stage and also post-treatment. The patients were categorized as patients with compound and heterozygous mutations as well as patients with rare and frequent attacks. To evaluate the frequent attack we used the criteria proposed by Pras et al.⁸ Patients with malnutrition, active infection, or using a zinc supplement were excluded.

Statistical Analysis

The study data underwent analysis using the SPSS (Statistical Package for Social Science) 27.0 software package. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Differences between the continuous variables in the two groups were evaluated using the Student's t-test. Differences in proportions were evaluated using the Chi-square test. Correlations between parameters were assessed using Pearson/Spearman correlation tests. The level of significance was set at $p < 0.05$.

RESULTS

One hundred twelve FMF patients (M/F=52/60) with a mean age of 11.9 ± 5.1 years who presented to the pediatric nephrology/rheumatology clinic were included in this study. 35 (31.3%) of the patients have compound heterozygous mutation and 77 (68.8%) have heterozygous mutation. There was no difference between the mutation groups in mean of gender and age ($p=0.358$ and $p=0.182$, respectively).

Both pre and post-treatment CRP and sedimentation levels were higher in the compound mutation group than in the heterozygous group ($p < 0.05$). However there was no difference in mean of leucocyte count and zinc level between these mutation groups (Table 1).

Table 1. Comparison of the mutation groups

Variable	Heterozygous n=77	Compound n=35	p-value
Gender (male) n (%)	38 (49.4)	14 (40)	0.358
Mean age at diagnosis* (year)	8.3 ± 4.4	7.0 ± 4.4	0.182
CRP** (mg/dl)			
Pre-treatment	2.1 (0.05-121.6)	39 (0.5-250.4)	<0.001
Post-treatment	0.6 (0.03-139)	3 (0.2-160)	<0.001
Sedimentation (mm/hr)**			
Pre-treatment	17 (3-98)	35 (7-129)	<0.001
Post-treatment	13 (2-114)	21 (4-68)	0.011
Leucocyte count (/10³)**			
Pre-treatment	7930 (4230-23680)	9450 (4480-23820)	0.159
Post-treatment	7820 (4850-20250)	8045 (4220-14560)	0.929
Zinc (µg/dl)*			
Pre-treatment	100.9 ± 22.0	98.3 ± 19.6	0.667
Post-treatment	102.4 ± 16.7	104.1 ± 14.0	0.704

CRP: C-reactive protein, *Mean±Standard deviation, **Median (minimum-maximum)

The mean pre-treatment sedimentation was significantly higher in patients with frequent attacks ($p=0.021$). However there was no difference between the attack frequency groups in mean of gender age, both of pre and post-treatment CRP, zinc, leucocyte count and post-treatment sedimentation ($p > 0.05$) (Table 2).

Leucocyte count, CRP, Zinc, Sedimentation averages were obtained for correlation analysis. There was a positive correlation between mean zinc and mean leucocyte

Table 2. Comparison of attack frequency groups

Variable	Rare attacks n=22	Frequent attacks n=90	p-value
Gender (male) n (%)	13 (59)	45 (50)	0.487
Mean age at diagnosis (year)*	7.5 ± 4.7	7.7 ± 4.3	0.907
CRP (mg/dl)**			
Pre-treatment	4.5 (0.1-106)	4.2 (0.1-212)	0.725
Post-treatment	0.5 (0.2-149)	1.1 (0.1-69.5)	0.481
Sedimentation (mm/hr)**			
Pre-treatment	11 (5-40)	25 (4-83)	0.021
Post-treatment	11 (5-68)	14 (2-47)	0.419
Leucocyte count (/10³)**			
Pre-treatment	8130 (4480-16700)	8300 (4230-23820)	0.953
Post-treatment	8320 (4850-13210)	7550 (4600-20250)	0.382
Zinc (µg/dl) **			
Pre-treatment	110.67 ± 21.8	99.0 ± 16.8	0.147
Post-treatment	97.5 ± 15.4	104.4 ± 14.1	0.187

CRP: C-reactive protein, *Mean±Standard deviation, **Median (minimum-maximum)

count, CRP levels ($p=0.019$, $r=0.334$ and $p=0.016$, $r=0.344$ respectively), but not with sedimentation. There was positive correlation between sedimentation, leucocyte count, CRP, within each parameter (Table 3).

Table 3. Correlation of zinc with the mean acute phase reactants

Variable	Leucocyte	Sedimentation	CRP	Zinc
Leucocyte count		$p < 0.001$ $r=0.481$	$p < 0.001$ $r=0.463$	$p=0.019$ $r=0.334$
Sedimentation	$p < 0.001$ $r=0.481$		$p < 0.001$ $r=0.568$	$p=0.133$ $r=0.222$
CRP	$p < 0.001$ $r=0.463$	$p < 0.001$ $r=0.568$		$p=0.016$ $r=0.344$
Zinc	$p=0.019$ $r=0.334$	$p=0.133$ $r=0.222$	$p=0.016$ $r=0.344$	

CRP: C-reactive protein

DISCUSSION

In this study, we evaluated zinc levels in patients with FMF and investigated their association with inflammatory markers. This study appears to be one of the first to investigate zinc levels in pediatric patients with FMF.

Oxidative stress is known to contribute to the inflammatory episodes observed in FMF.⁹ Trace elements like zinc are crucial for defending cells and tissues against damage caused by free radicals.¹⁰ A decline in these elements can impair antioxidant defenses. Nevertheless, there is still limited understanding of how trace elements influence the inflammatory flares seen in FMF.

We did not find a significant difference between zinc levels, either in mutation groups and attack groups. Likely in a study comparing rheumatoid arthritis and osteoarthritis found no significant differences in zinc concentrations in plasma and synovial fluid between the patients groups and control groups.¹¹

We observed a positive correlation between zinc levels and CRP, leucocyte counts. Several studies have explored the link between dietary zinc and inflammatory markers. In the U.S., research involving healthy individuals identified a notable positive association between zinc intake and

CRP concentrations.² Similarly, Jung et al.¹² showed a comparatively clearer linear association was observed between serum zinc concentrations and inflammatory markers particularly in women. Conversely, investigations among older adults in Brazil found a negative correlation between serum zinc levels and CRP.³ Our interpretation emphasized that zinc may act as an acute-phase reactant under specific inflammatory conditions such as FMF, rather than serving as a simple anti-inflammatory indicator. We suggest that zinc concentrations may fluctuate in parallel with inflammatory activity, but this does not imply a causal relationship or confirm that zinc behaves as an acute-phase reactant.

Although zinc is generally described as inversely related to inflammatory activity, our finding of a positive correlation between zinc and CRP in FMF may reflect disease-specific metabolic responses rather than a simple anti-inflammatory relationship. During acute inflammatory episodes, cytokine-driven induction of metallothionein and hepatic redistribution of zinc can transiently alter serum zinc concentrations.¹³ In addition, frequent inflammatory attacks and colchicine therapy may modify zinc kinetics, leading to short-term elevations in circulating zinc despite chronic intracellular depletion.¹⁴ These mechanisms could explain the observed positive association without implying that zinc promotes inflammation.

Limitations

An important limitation of our study was, measurements of acute phase reactant and zinc were taken at two time points (pre and post-treatment); including more time points would have added value to our study. This factor restricts the ability to infer causality and generalize the findings. Nevertheless, this study is one of the first pediatric studies to investigate the association between zinc status and inflammatory markers in FMF.

CONCLUSION

Notably, in our current study, serum zinc levels were positively associated with inflammatory markers in FMF patients. Further research is required to explore the exact mechanisms connecting zinc and inflammation, and may also help to evaluate the effects of zinc supplementation in patients with FMF.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethics committee approval of the study was obtained from the Kırıkkale University Clinical Researches Ethics Committee (Date: 25.06.2025, Decision No: 2025.25.08).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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