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Research Article

The Role of Serum Zinc, Iron, Magnesium, and Selenium Levels in the Pathogenesis of PFAPA Syndrome

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ABSTRACT

Objective: To investigate the potential role of zinc, iron, magnesium, and selenium in the pathogenesis of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome.

Methods: A retrospective analysis was conducted of 26 children diagnosed with PFAPA and 31 age- and sex-matched healthy controls. Serum levels of zinc, iron, magnesium, and selenium were retrieved from hospital records and compared between the groups.

Results: Magnesium levels were 2.03 ± 0.14 mg/dL in the PFAPA group and 1.99 ± 0.13 mg/dL in the control group. The difference was not statistically significant (P = 0.308). Median iron levels (25^{th}-75^{th} percentiles) were 52.5 µg/dL (22.0-81.5) in the PFAPA group and 61.1 µg/dL (42.5-89.0) in the control group; the difference was not significant (P = 0.226). Zinc levels were similar: 86.24 ± 11.18 mcg/L in the PFAPA group and 87.26 ± 10.06 mcg/L in the control group (P = 0.720). However, median selenium levels differed significantly: 38.9 mcg/L (34.2-50.0) in the PFAPA group versus 48.0 mcg/L (43.0-55.5) in the control group (P = 0.002). Each one-unit increase in selenium levels increased the odds of disease by approximately 8.6%, and this association was statistically significant (odds ratio = 1.086, 95% confidence interval: 1.019-1.157, P = 0.011).

Conclusion: In conclusion, this study demonstrates that low selenium levels are associated with PFAPA syndrome in children. No significant relationships were observed between zinc, iron, or magnesium levels and the disease. Given the effects of selenium on the immune system and inflammation, we hypothesize that selenium deficiency may contribute to the pathogenesis of PFAPA.

Keywords: Periodic fever, autoinflammatory, selenium, zinc, magnesium

INTRODUCTION

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome, characterized by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis is an autoinflammatory disease first described by Marshall et al.[1] in 1987.[2] PFAPA is the most widespread cause of periodic fever in childhood, although the true incidence is unknown.[3] There is no specific laboratory finding or diagnostic test for the syndrome.[2] Although the clinical manifestations have been well described, the lack of a disease-specific laboratory finding makes diagnosis difficult. Diagnosis is therefore based on clinical criteria, with the modified Marshall criteria most frequently employed. According to these criteria, periodic fever attacks commencing before five years of age, aphthous stomatitis without upper respiratory tract infection, pharyngitis or cervical lymphadenitis, being asymptomatic between attacks, exclusion of cyclic neutropenia, and normal growth and development are regarded as diagnostic.[4]

Zinc, iron, magnesium, and selenium are elements with important functions. Zinc is an essential trace element for biological processes and serves as a cofactor for more than 300 enzymes involved in protein synthesis and repair systems. It is also involved in cellular signaling at all levels and plays an

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important role in immune system regulation.[5] Although the principal function of iron is the transport of O_2 by hemoglobin, it is also an important cofactor for several enzymes and plays a critical role in the immune system and in defense against infection.[6] Selenium is an important micronutrient for human health, particularly through its effects on thyroid metabolism, the cardiovascular system, and the immune system. It is involved in the activation, proliferation, and differentiation of cells that direct immune responses and contributes to immune regulation by preventing excessive responses that could lead to autoimmunity or chronic inflammation.[7] Finally, magnesium is an important element in the regulation of metabolism and homeostasis in all tissues. It regulates ion channel activity, acts as a second messenger in signal transmission, contributes to the production of adenosine triphosphate, and influences immunological functions by affecting immune cells.[8]

PFAPA syndrome has long been recognized. Several potential etiological factors have been investigated, including infectious agents, immunological mechanisms, and genetic predisposition; however, the disease's etiopathogenesis and genetic basis remain unclear.[9] The purpose of this study was to investigate the potential role of zinc, iron, magnesium, and selenium, all of which are involved in immune function, in the pathogenesis of PFAPA.

MATERIAL AND METHODS

Approval for the study was obtained from the Kastamonu University Clinical Research Ethics Committee prior to commencement (decision no.: 2023-KAEK-106, date: 13.09.2023). All procedures in studies involving human participants are carried out in accordance with institutional ethical standards (Kastamonu Ethical Committee) and with the 1964 Declaration of Helsinki. Informed consent was not obtained because the study was conducted retrospectively.

This retrospective study included 26 patients diagnosed with PFAPA who were under follow-up at the Kastamonu Training and Research Hospital Ear, Nose, and Throat Clinic (Türkiye) between 01.09.2021 and 01.09.2023, and 31 age- and sex-matched healthy controls. Test results obtained during the follow-up periods were retrieved retrospectively from the hospital records, and zinc (70-115 mcg/L), iron (16-129 µg/dL), magnesium (1.7-2.3 mg/dL), and selenium (46-143 mcg/L) levels were recorded. The obtained data were then compared with data from the healthy control group. Patients with acute bacterial infection, autoimmune diseases, or anemia were excluded.

MAIN POINTS

- Serum selenium levels were significantly lower in children with Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome compared to healthy controls.
- Each unit increase in selenium concentration was associated with an 8.6% lower risk of PFAPA, suggesting a potential protective role for selenium.
- No significant differences were observed in serum zinc, iron, and magnesium levels between PFAPA patients and controls.
- Low selenium levels may contribute to immune dysregulation and excessive inflammatory responses in the pathogenesis of PFAPA.
- Selenium supplementation may represent a therapeutic approach, but further prospective studies are required.

Statistical Analysis

Normality of the study data distribution was assessed using histograms, Q-Q plots, and the Shapiro-Wilk test. Quantitative variables were compared between the groups using the Mann-Whitney U test and paired samples t-test, while relationships between categorical variables were evaluated using the chi-square test. Univariate logistic regression analysis was applied to evaluate potential risk factors affecting the disease. The analysis results were reported as odds ratios (ORs) with 95% confidence interval (CI). *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean ages of the PFAPA and control groups were 7.12 ± 2.25 and 6.97 ± 2.34 years, respectively; no significant difference was observed between them (*P* = 0.810). In terms of gender distribution, girls comprised 46.2% and boys 53.8% of the PFAPA group, compared with 45.2% and 54.8% in the control group. No significant difference in gender distribution was observed between groups (*P* = 0.999).

Regarding biochemical parameters, magnesium levels were 2.03 ± 0.14 mg/dL in the PFAPA group and 1.99 ± 0.13 mg/dL in the control group. The difference was not statistically significant (*P* = 0.308). Median iron levels (25^{th}-75^{th} percentile) were 52.5 µg/dL (22.0-81.5) in the PFAPA group and 61.1 µg/dL (42.5-89.0) in the control group, the difference also being insignificant (*P* = 0.226). Zinc levels were also similar, at 86.24 ± 11.18 mcg/L in the PFAPA group and 87.26 ± 10.06 mcg/L in the control group (*P* = 0.720). However, median selenium levels differed significantly, at 38.9 mcg/L (34.2-50.0) in the PFAPA group and 48.0 mcg/L (43.0-55.5) in the control group (*P* = 0.002) (Figure 1). The groups' demographic characteristics and biochemical parameters are summarized in Table 1.

In univariate regression analysis, magnesium levels exhibited a protective effect against the disease; however, this association was not statistically significant (OR = 0.119, 95% CI: 0.002-6.966, *P* = 0.305). Similarly, no significant association was observed between iron levels and the disease (OR = 1.007, 95% CI: 0.992-1.022, *P* = 0.360). Zinc levels also exhibited no significant association (OR = 1.009, 95% CI: 0.960-1.062, *P* = 0.714). However, a significant relationship was observed between selenium levels and the disease. Each one-unit increase in selenium levels increased the odds of disease by approximately 8.6%, and this association was statistically significant (OR = 1.086, 95% CI: 1.019-1.157, *P* = 0.011) (Table 2).

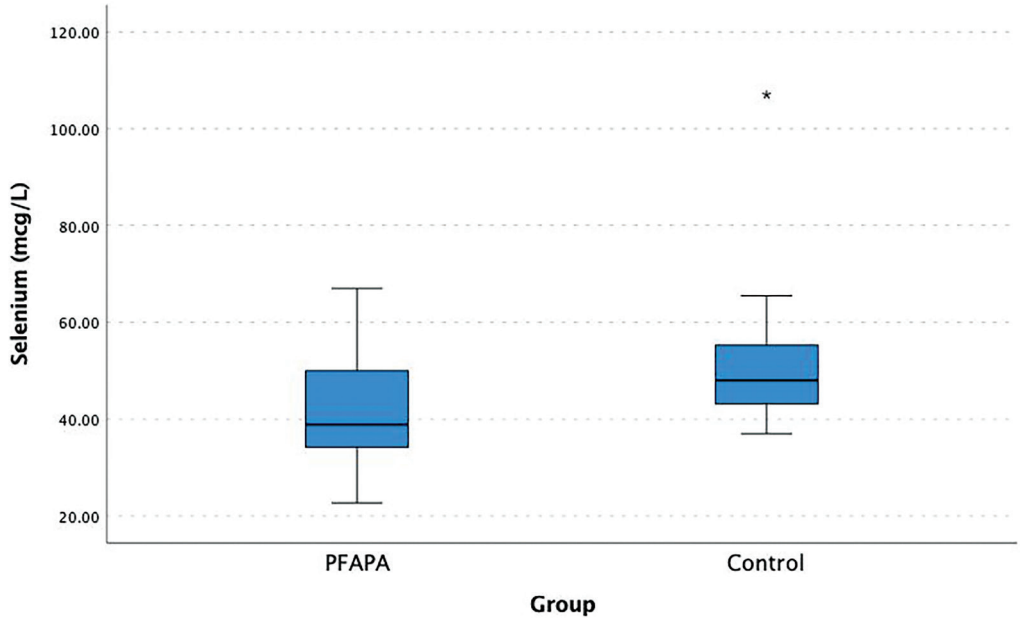

Figure 1. Box plot of selenium levels in the PFAPA and control groups.
PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis.

Table 1. The Groups' Demographic Characteristics and Biochemical Parameters

Variables	Group		*P*
	PFAPA (n=26)	Control (n=31)	
Age	7.12 ± 2.25	6.97 ± 2.34	0.810
Gender			
Female	12 (46.2)	14 (45.2)	0.999
Male	14 (53.8)	17 (54.8)	
Magnesium	2.03 ± 0.14	1.99 ± 0.13	0.308
Iron	52.5 (22.0-81.5)	61.1 (42.5-89.0)	0.226
Zinc	86.24 ± 11.18	87.26 ± 10.06	0.720
Selenium	38.9 (34.2-50.0)	48.0 (43.0-55.5)	**0.002**

Data expressed as n (%), mean ± standard deviation, and median (25^{th}-75^{th} percentile) values.
PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis.

Table 2. Analysis of Risk Factors Affecting the Disease

Variables	Univariate	
	OR (95% CI)	*P*
Magnesium	0.119 (0.002-6.966)	0.305
Iron	1.007 (0.992-1.022)	0.360
Zinc	1.009 (0.960-1.062)	0.714
Selenium	1.086 (1.019-1.157)	**0.011**

OR, odds ratio; CI, confidence interval.

DISCUSSION

Serum selenium levels in this study were significantly lower in children with PFAPA syndrome than in the control group, and an increase in selenium levels was associated with a reduced risk of the disease. This finding is consistent with the known anti-inflammatory and regulatory effects of selenium on the immune system and suggests that it may play a role in the etiopathogenesis of PFAPA syndrome.[7,10-12] Huang et al. [7] examined the role of selenium in inflammation and immunity and reported that selenium levels were important for initiating immunity and also played a role in regulating excessive immune responses and chronic inflammation. Similarly, Hariharan and Dharmaraj[10] emphasized the antioxidant and anti-inflammatory effects of selenoproteins and concluded that glutathione peroxidase assisted in controlling excessive free-radical production at the site of inflammation. Navarro Garcia et al.[11] emphasized selenium's neuroprotective and anti-inflammatory properties and showed that it may be beneficial in various inflammatory states. Osuna-Padilla et al.[12] also reported that selenium supplementation reduced immune activation and inflammation in individuals infected with human immunodeficiency virus.

PFAPA syndrome is an autoinflammatory disease of uncertain etiology.[13-15] Overactivation of the innate immune system and of proinflammatory cytokines has been implicated in the pathogenesis.[13] The low selenium levels observed in the present study suggest that either selenium requirements may have increased to counteract the heightened inflammatory response and oxidative stress in patients with PFAPA syndrome or that selenium deficiency may contribute to these inflammatory processes. Considering the role of selenium in immune regulation, low selenium levels may be either a cause or a result of the excessive immune response observed in PFAPA syndrome. This, in turn, suggests that selenium supplementation may represent a potential therapeutic approach for the management of the syndrome. However, more extensive prospective studies are now needed to confirm that hypothesis.

No significant associations were determined between zinc, iron, or magnesium levels and PFAPA syndrome in this study. However, in light of the general effects of these elements on the immune system and inflammation, their potential roles in the pathogenesis of PFAPA still merit investigation. Sanna et al.[5] examined the relationship between zinc and autoimmunity and reported that zinc deficiency can impair the function of immune cells and affect inflammatory responses. Although the principal function of iron is oxygen transport, it also plays a critical role in immune function and defense against infection.[6] Brock and Mulero[6] examined the cellular and molecular aspects of iron and reported that iron deficiency or excess can affect immune responses. No significant difference in iron levels between the two groups was detected in the present study. This suggests that iron plays no direct role in the pathogenesis of PFAPA. However, inflammatory conditions can affect iron metabolism.

Magnesium is an important element involved in the regulation of homeostasis and metabolism of all tissues. It also affects immune cells by regulating immune functions.[16] Maier et al. [8] reported that magnesium deficiency activated phagocytes and triggered inflammation by increasing cytokine production. Low magnesium levels have therefore been linked to various chronic inflammatory diseases. Although no significant difference in magnesium levels was observed in the present study, its role in PFAPA requires more detailed examination in light of the potent effects of magnesium on inflammation. In particular, vitamin D deficiency has been shown to be associated with PFAPA, and magnesium is an important cofactor in vitamin D metabolism.[17,18] Future studies should therefore assess the interaction between magnesium and vitamin D in the pathogenesis of PFAPA.

Study Limitations

The principal limitations of this study are its retrospective design and relatively small sample size. Although the low selenium levels represent an important finding, further prospective, randomized controlled studies are needed to establish whether this relationship is causal or consequential. Future studies should evaluate the effects of selenium supplementation on the frequency, severity, and duration of PFAPA syndrome and establish the safety and efficacy of such supplementation. In addition, the effects of other trace elements such as zinc, iron, and magnesium on inflammatory markers and cytokine profiles might be investigated. Further, more extensive studies investigating the role of genetic and immunological parameters and environmental factors are needed to better understand the etiopathogenesis of PFAPA syndrome.

CONCLUSION

In conclusion, this study shows that low selenium levels in children with PFAPA syndrome are related to the disease. No significant relationships were determined between zinc, iron, or magnesium levels and the disease. Considering the effects of selenium on the immune system and inflammation, we think that selenium deficiency may play a role in the pathogenesis of PFAPA.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Kastamonu University Clinical Research Ethical Committee (decision no.: 2023-KAEK-106, date: 13.09.2023).

Informed Consent: Retrospective study. Permission was obtained from hospital management to collect study data from the Information Management System.

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Footnotes

Author Contributions

Concept Design – F.A.; Data Collection or Processing – F.A.; Analysis or Interpretation – F.A.; Literature Review – M.Y.; Writing, Reviewing and Editing – F.A., M.Y.

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REFERENCES

1. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr*. 1987;110(1):43-46. [CrossRef]
2. Onur H, Onur AR. Diagnostic performance of routine blood parameters in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. *J Clin Lab Anal*. 2023;37(11-12):e24934. [CrossRef]
3. Lazea C, Damian L, Vulturar R, Lazar C. PFAPA syndrome: clinical, laboratory and therapeutic features in a single-centre cohort. *Int J Gen Med*. 2022;15:6871-6880. [CrossRef]
4. Hausmann J, Dedeoglu F, Broderick L. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome and syndrome of unexplained recurrent fevers in children and adults. *J Allergy Clin Immunol Pract*. 2023;11(6):1676-1687. [CrossRef]
5. Sanna A, Firinu D, Zavattari P, Valera P. Zinc status and autoimmunity: a systematic review and meta-analysis. *Nutrients*. 2018;10(1):68. [CrossRef]
6. Brock JH, Mulero V. Cellular and molecular aspects of iron and immune function. *Proc Nutr Soc*. 2000;59(4):537-540. [CrossRef]
7. Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. *Antioxid Redox Signal*. 2012;16(7):705-743. [CrossRef]
8. Maier JA, Castiglioni S, Locatelli L, Zocchi M, Mazur A. Magnesium and inflammation: advances and perspectives. *Semin Cell Dev Biol*. 2021;115:37-44. [CrossRef]
9. Yıldız M, Haslak F, Adrovic A, et al. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: a single-center experience. *Turk Arch Pediatr*. 2022;57(1):46-52. [CrossRef]
10. Hariharan S, Dharmaraj S. Selenium and selenoproteins: it's role in regulation of inflammation. *Inflammopharmacology*. 2020;28(3):667-695. [CrossRef]
11. Navarro Garcia E, Leon S, Alvarez Toledo N. Selenium's role in neuroprotection against stroke-induced inflammation. *Cureus*. 2024;16(1):e52205. [CrossRef]
12. Osuna-Padilla IA, Rodríguez-Moguel NC, Aguilar-Vargas A, et al. Zinc and selenium supplementation on treated HIV-infected individuals induces changes in body composition and on the expression of genes responsible of naïve CD8+ T cells function. *Front Nutr*. 2024;11:1417975. [CrossRef]
13. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A, Wekell P. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. *Pediatr Rheumatol Online J*. 2022;20(1):82. [CrossRef]
14. Tekin M, Toplu Y, Kahramaner Z, et al. The mean platelet volume levels in children with PFAPA syndrome. *Int J Pediatr Otorhinolaryngol*. 2014;78(5):850-853. [CrossRef]
15. Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP. Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst Rev*. 2019;12(12):CD008669. [CrossRef]
16. Stefanache A, Lungu II, Butnariu IA, et al. Understanding how minerals contribute to optimal immune function. *J Immunol Res*. 2023;2023:3355733. [CrossRef]
17. Nalbantoğlu A, Nalbantoğlu B. Vitamin D deficiency as a risk factor for PFAPA syndrome. *Int J Pediatr Otorhinolaryngol*. 2019;121:55-57. [CrossRef]
18. Faydhi SA, Kanawi HMA, Al-Khatib T, Zawawi F. The association between vitamin D level and PFAPA syndrome: a systematic review. *Indian J Otolaryngol Head Neck Surg*. 2022;74(Suppl 3):5548-5555. [CrossRef]