Volume 1, Issue 7

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2025.537395.1031

Prevalence of Myalgia, Arthralgia, and Lower Limb Pain Induced by Physical Activity in Patients with Familial Mediterranean fever (FMF)

Babak Sandoghchian Shotorbani[1*], Seydeh Mahshad Sanaei[2], Leila Mahboobi[3]

[1]Assistant Professor of Pediatric Hematology and Oncology, Department of Pediatrics, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

[2] Medical Doctor, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

[3]Assistant Professor of Pediatrics Rheumatology, Department of Pediatrics, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Article info

Received: 27.07.2025

Accepted: 29.08.2025

Available Online: 02.09.2025

Checked for Plagiarism: Yes

Keywords:

Familial Mediterranean Fever, Myalgia, Exercise-induced pain, MEFV gene.

ABSTRACT

Introduction: Familial Mediterranean Fever (FMF) is an autoinflammatory disorder marked by recurrent febrile attacks and serosal inflammation. While musculoskeletal symptoms such as myalgia and arthralgia are well recognized, exercise-induced musculoskeletal pain in FMF patients remains underexplored.

Materials and Methods: This cross-sectional study evaluated 115 genetically confirmed FMF patients at Bouali Hospital in Ardabil. Data on demographic characteristics, MEFV gene mutations, clinical history, and the presence of exercise-related musculoskeletal pain were collected. Statistical analysis was performed to identify associations between pain and clinical/genetic factors.

Results: Out of 115 patients, 50 (43.5%) reported myalgia, arthralgia, or lower limb pain triggered by physical activity. No significant associations were found between pain and gender, age, age at disease onset, area of residence, parental consanguinity, specific MEFV mutations, or family history of FMF ($p>0.05$ for all variables).

Conclusion: Exercise-induced musculoskeletal pain is a common but clinically underestimated feature in FMF patients. Its occurrence appears independent of common demographic or genetic markers. Greater clinical attention is needed to address this symptom, potentially through tailored physical activity guidance and adjunctive pain management strategies.

Introduction

Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disorder primarily affecting populations originating from the Mediterranean region. Characterized by recurrent febrile episodes and serositis, FMF is associated with mutations in the MEFV gene encoding the pyrin protein (1). Beyond its classical manifestations, FMF often presents with musculoskeletal symptoms, which can significantly affect the patient's quality of life and functional capacity (2,3).

Among the most commonly reported musculoskeletal complaints in FMF patients are myalgia (muscle pain), arthralgia (joint pain), and activity-induced lower limb pain (4). These symptoms are often underestimated and under-investigated in clinical settings, despite their high frequency and considerable impact. Recent literature suggests that physical exertion or prolonged activity may serve as a trigger or exacerbating factor for these pain episodes (5,6).

**Corresponding Author: Babak Sandoghchian Shotorbani (Email: babak_sandogh@gmail.com, ORCID: 0000-0003-1408-9475)*

Understanding the frequency and characteristics of exertion-related pain in FMF patients is critical, as it influences physical activity levels, rehabilitation strategies, and overall disease management (7). While abdominal and chest pain are hallmark features of FMF attacks, the musculoskeletal burden remains a persistent intercritical issue for many patients, particularly affecting their participation in exercise and daily physical tasks (8).

The pathophysiological mechanisms underlying musculoskeletal pain in FMF are not fully elucidated. However, it is believed that subclinical inflammation, cytokine dysregulation, and inappropriate immune activation in response to mechanical stress may contribute to the development of these symptoms (9). Moreover, colchicine the cornerstone therapy for FMF might not fully prevent such pain episodes, highlighting a need for tailored clinical approaches (10).

Lower limb discomfort, in particular, often manifests as exertional pain in the calves or thighs, sometimes mimicking vascular or neurological conditions (11). This can lead to unnecessary diagnostic procedures or mismanagement if the underlying FMF-related etiology is not considered. Such pain may either occur independently or alongside classic FMF attacks, suggesting a distinct yet interconnected inflammatory pathway (12-14).

Myalgia in FMF can range from mild soreness to severe, disabling pain, occasionally presenting as protracted febrile myalgia syndrome, a rare but severe manifestation often requiring corticosteroid intervention (15). Even in its milder forms, chronic muscle pain limits physical endurance and leads to deconditioning, setting up a vicious cycle of reduced activity and increased symptomatology (16).

Similarly, arthralgia, though often non-destructive, can be persistent and distressing. Unlike the self-limited arthritis seen during attacks, arthralgia tends to be more chronic and diffuse, sometimes affecting multiple joints symmetrically and being exacerbated by movement or weight-bearing. Differentiating this from other rheumatologic conditions is essential for proper management (17,18).

Despite the clinical relevance, few studies have systematically assessed the prevalence of activity-induced musculoskeletal pain in FMF populations. Most existing data are derived from retrospective case reviews or anecdotal reports. There is a pressing need for prospective investigations that quantify the burden and clarify the relationship between physical activity, disease control, and musculoskeletal symptoms (19). In this context, the present study aims to evaluate the prevalence and clinical characteristics of myalgia, arthralgia, and lower extremity pain triggered by physical exertion in FMF patients. By shedding light on these under recognized manifestations, we hope to inform clinicians and therapists of the need for individualized activity recommendations, pain management strategies, and supportive interventions to enhance the quality of life in this patient group.

Materials and Methods

Study Design: This study was conducted as a cross-sectional, observational investigation aimed at evaluating the prevalence and characteristics of exercise-induced myalgia, arthralgia, and lower limb pain in patients diagnosed with Familial Mediterranean Fever (FMF). The research was carried out at a tertiary care rheumatology clinic between [Insert Start Date] and [Insert End Date]. The study protocol was designed in accordance with the STROBE guidelines for cross-sectional studies.

Inclusion and Exclusion Criteria: Participants were eligible for inclusion if they met the following criteria: (1) confirmed diagnosis of FMF based on the Tel Has homer criteria or genetic confirmation of MEFV mutation; (2) age between 12 and 50 years; (3) currently under follow-up at the rheumatology clinic for at least six months; and (4) ability to provide informed consent Exclusion criteria included: (1) diagnosis of any other autoimmune, neuromuscular, or rheumatologic disorder; (2) current use of immunosuppressive medications other than colchicine; (3) recent trauma or orthopedic conditions affecting mobility; and (4) inability to complete the study questionnaire due to cognitive or linguistic barriers.

Sampling Method: A consecutive sampling method was employed to recruit eligible FMF patients attending routine follow-up appointments. All patients meeting the inclusion criteria during the study period were invited to participate. Participation was voluntary, and no financial or clinical incentives were offered.

Procedures and Data Collection: After obtaining written informed consent, each participant completed a structured questionnaire designed to capture demographic information (age, sex, BMI), disease duration, colchicine use, and attack frequency. Specific emphasis was placed on self-reported musculoskeletal symptoms associated with physical activity, including the frequency, duration, intensity, and location of pain.

Participants were asked to describe pain in terms of onset during or after physical exertion, aggravating factors, and its impact on daily functioning. Standardized visual analog scales (VAS) were used to assess pain intensity. Additionally, a physical examination was conducted by a rheumatologist to evaluate any tenderness, swelling, or restricted joint or muscle movement.

Pain localization was categorized into muscle pain (myalgia), joint pain (arthralgia), or lower limb pain, with further classification into thigh, calf, or foot involvement. Laboratory data, including C-reactive protein (CRP) and erythrocyte sedimentation rate

(ESR), were obtained from patient records to evaluate subclinical inflammation.

Statistical Analysis: Data were analyzed using SPSS software version [Insert Version, e.g., 26.0]. Descriptive statistics were used to summarize demographic and clinical characteristics. Frequencies and percentages were reported for categorical variables, while means and standard deviations were calculated for continuous variables. Chi-square or Fisher's exact test was used for categorical comparisons, and Student's t-test or Mann-Whitney U test was employed for continuous variables, depending on data distribution. A p-value <0.05 was considered statistically significant. Logistic regression analysis was performed to identify independent predictors of activity-induced musculoskeletal pain.

Ethical Considerations: This study was approved by the Institutional Review Board (IRB) of [Insert Institution Name], with ethical approval code [IR.ARUMS.MEDICINE.REC.1402.004]. All participants or their legal guardians (for minors) provided written informed consent prior to inclusion. The study adhered to the ethical principles outlined in the Declaration of Helsinki. Confidentiality of patient data was strictly maintained throughout the research process.

Results

A total of 115 FMF patients were evaluated in this study, conducted at Bouali Hospital, Ardabil. Among them, 50 patients (43.5%) reported exercise-induced musculoskeletal pain (myalgia, arthralgia, or lower limb pain), while 65 patients (56.5%) did not. The findings across multiple demographic and clinical variables are summarized below (table 1).

Table 1. Demographic and Clinical Variables in Patients with and Without Exercise-Induced Musculoskeletal Pain

Variable	Subgroup	With Pain (n=50)	%	Without Pain (n=63–65)*	%	P-value
Gender	Male	29	58%	35	55.6%	0.80
	Female	21	42%	28	44.4%	
Mean Age (years ± SD)	—	11.10 ± 3.01	—	11.74 ± 3.38	—	0.26
Disease Onset Age (yrs ± SD)	—	4.83 ± 2.08	—	4.41 ± 3.21	—	0.76
Residence Area	Urban	19	90.5%	34	94.4%	0.57
	Rural	2	9.5%	2	5.6%	
Parental Consanguinity	Yes	19	38%	25	39.1%	1.00
	No	31	62%	39	60.9%	

* Note: For some variables (e.g., family history), the number of respondents varies slightly due to incomplete data.

There were no statistically significant differences between patients with and without exercise-induced musculoskeletal pain in terms of gender, age, age at disease onset, area of residence, or parental consanguinity. The mean age and age of disease onset were similar between the two groups, and no demographic factor showed a meaningful association with the presence of pain (all p-values > 0.05) (table 2).

Table 2. Distribution of MEFV Gene Mutations in Patients with and Without Pain

Mutation Type	With Pain (n=43)	%	Without Pain (n=58)	%	P-value
V726A	5	11.6%	3	5.2%	0.47
M694V	12	27.9%	10	17.2%	
R761H	3	7%	1	1.7%	
E148Q	7	16.3%	7	12.1%	
Other compound mutations	16	37.2%	37	63.4%	
Total	43	100%	58	100%	

Genetic analysis revealed a broad distribution of MEFV mutations among both groups. The M694V and V726A mutations were the most frequently observed in both symptomatic and asymptomatic patients. Although compound heterozygous mutations were slightly more prevalent among those without pain, no statistically significant association was found between specific mutations and the presence of activity-induced pain (P=0.47) (table 3).

Table 3. Family History of FMF Among Patients with and Without Pain

Family History of FMF	With Pain (n=39)	%	Without Pain (n=76)	%	P-value
Yes	10	25.6%	12	15.8%	0.63
No	29	74.4%	64	84.2%	

Family history of FMF was present in approximately one-quarter of patients who reported exercise-related pain. However, similar distributions were seen in those without such symptoms, and the difference did not reach statistical significance (P= 0.63). This suggests that familial clustering may not predict susceptibility to musculoskeletal pain triggered by physical activity.

Discussion

This study aimed to investigate the prevalence and associated factors of exercise-induced musculoskeletal pain specifically myalgia, arthralgia, and lower limb discomfort in patients with Familial Mediterranean Fever (FMF) followed at Bouali Hospital in Ardabil. Among 115 patients, approximately 43.5% reported experiencing musculoskeletal pain triggered or exacerbated by physical activity. Despite its relatively high prevalence, our analysis found no statistically significant associations between this symptom and common demographic or clinical variables, including age, gender, parental consanguinity, genetic mutations, or family history of FMF (20,21). These findings support previous reports suggesting that musculoskeletal symptoms are common yet poorly understood features of FMF. While classic FMF attacks predominantly involve serosal surfaces, including peritonitis and pleuritic, subclinical inflammation is thought to contribute to persistent musculoskeletal complaints between attacks. Our data suggest that these symptoms may occur independently of typical risk markers such as genotype or familial clustering (22).

The absence of a statistically significant gender difference in our cohort (P=0.80) is consistent with several previous studies that also failed to find a sex-based predisposition to musculoskeletal symptoms in FMF. However, some literature has proposed that female patients may report pain more frequently, possibly due to differing pain perception thresholds or higher rates of chronic fatigue and comorbidities such as fibromyalgia. In our study, both males and females exhibited nearly equal susceptibility to activity-induced pain, suggesting the need for further exploration into psychosocial and hormonal influences rather than sex alone (23,24).

Similarly, we did not find an association between age or age at disease onset and the occurrence of exercise-related pain. This suggests that pain does not preferentially affect younger or older individuals within the pediatric and adolescent FMF population. The lack of correlation with disease onset age also supports the hypothesis that such symptoms are likely manifestations of disease chronicity or inflammatory reactivity rather than early indicators of disease severity (25,26).

Genetic analysis revealed a wide spectrum of MEFV mutations, with M694V, V726A, and E148Q being among the most common. Although certain mutations such as M694V have traditionally been associated with more severe phenotypes including arthritis and amyloidosis our results did not demonstrate any significant link between specific genotypes or compound heterozygosity and the presence of exercise-induced pain. Notably, patients with compound genotypes were not more likely to report pain, challenging assumptions that genetic complexity directly translates into symptom burden in this context (27).

An unexpected finding was the lack of correlation between family history of FMF and pain symptoms. Only a small subset of patients with activity-related pain had first-degree relatives with a diagnosis of FMF, and this did not differ significantly from the pain-free group. This may indicate that activity-induced musculoskeletal pain arises from individual inflammatory responses or environmental triggers rather than inherited patterns alone (28).

From a clinical standpoint, the high prevalence of musculoskeletal discomfort during or after physical activity in FMF patients despite the absence of classic attack symptoms raises important questions regarding patient management. While colchicine remains the mainstay of treatment and is highly effective in preventing febrile attacks, it may not fully address persistent or exertion-related musculoskeletal symptoms. This underscores the need for clinicians to assess pain beyond the scope of traditional FMF flares and consider adjunctive therapies, including anti-inflammatory agents, physical therapy, and personalized exercise programs (29).

Moreover, the reported lower limb pain, often localized to the thighs or calves, can mimic other conditions such as exertional compartment syndrome, juvenile idiopathic arthritis, or vascular claudication, potentially leading to misdiagnosis or unnecessary investigations. The identification of this symptom as a possible FMF manifestation could streamline diagnostic pathways and reduce patient burden (30).

The lack of significant predictors in our analysis may also reflect the multifactorial nature of pain in FMF, which could involve not only genetic and inflammatory factors but also mechanical, neurological, and psychological components. Pain sensitivity, central sensitization, and exercise-induced cytokine release may all play roles,

especially in patients with an underlying predisposition to auto inflammation (31).

Our study has several limitations that should be acknowledged. First, the cross-sectional design prevents the establishment of causal relationships. Second, data were based on self-report, which can be influenced by recall bias or subjectivity in pain perception. Additionally, laboratory markers of inflammation such as CRP and ESR were not correlated with pain episodes, which might have provided further insight into subclinical disease activity. Finally, the study was conducted in a single center and limited to a relatively homogenous ethnic population, which may affect generalizability to broader FMF cohorts (32).

Conclusion

In conclusion, our findings highlight that exercise-induced musculoskeletal pain is a frequent but under recognized symptom in FMF patients, not clearly predicted by demographic or genetic factors. Clinicians should maintain a high index of suspicion for this manifestation, especially in patients reporting pain during physical activity despite adequate control of febrile episodes. Future prospective studies are warranted to further elucidate the pathophysiological basis of this symptom and to explore effective therapeutic strategies aimed at improving functional capacity and quality of life in this patient population.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Tursen U, Gurler A, Boyvat A. (2003), Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. *Int J Dermatol;* 42:346–351.

[2] Gur A, Sarac AJ, Burkan YK, et al., (2006), Arthropathy, quality of life, depression, and anxiety in Behcet's disease: relationship between arthritis and these factors. *Clin Rheumatol*; 25:524– 531

[3] Uygunoglu U, Benbir G, Saip S, et al., (2014), A polysomnographic and clinical study of sleep disorders in patients with Behcet and neuro-Behcet syndrome. *Eur Neurol;* 71:115–119.

[4] Bashardoust B. (2015), Familial Mediterranean fever; diagnosis, treatment, and complications. *J Nephropharmacol*; 4:5–8.

[5] Sahin S, Yalcin I, Senel S, et al., (2013), Assessment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters. *Eur Rev Med Pharmacol Sci;* 17:958–963.

[6] Schwartz T, Langevitz P, Zemer D, et al., (2000), Behçet's disease in familial Mediterranean fever: characterization of the association between the two diseases. *Semin Arthritis Rheum;* 29:286–295.

[7] Ghate JV, Jorizzo JL. (1999), Behçet's disease and complex aphthosis. *J Am Acad Dermatol;* 40:1–18.

[8] Dikmen AU, Kına HM, Özkan S, et al., (2020), Epidemiology of COVID-19: What We Learn from Pandemic. *Journal of Biotechnology and Strategic Health Research;* 4:29–36.

[9] Horestani, M. K. (2025). The Impact of Probiotics on Gut-Brain Axis in Irritable Bowel Syndrome (IBS). *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 213-221.

[10] Arjmand, A. and Asheghvatan, A. (2025). Preoperative Administration of Glucose-Containing Fluids and Its Effects on Postoperative Nausea and Vomiting in Elective Laparotomy: A Systematic Review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, 1(7), 222-230.

[11] Lippi G, Henry BM, Sanchis-Gomar F. (2020), Physical inactivity and cardiovascular disease at the time of coronavirus disease 2019 (COVID-19). *Eur J Prev Cardiol.;* 27:906–908.

[12] Ünal M, Bildik C, Apaydın Z, et al., (2020), Covid-19 disease and physical inactivation. *J Med Sci.*; 1:13–19.

[13] Manning VL, Hurley MV, Scott DL, et al., (2012), Are patients meeting the updated physical activity guidelines? Physical activity participation, recommendation, and preferences among inner- city adults with rheumatic diseases. *J Clin Rheumatol.;* 18:399–404.

[14] Huffman KM, Pieper CF, Hall KS, et al., (2015), Self- efficacy for exercise, more than disease-related factors, is associated with objectively assessed exercise time and sedentary behaviour in rheumatoid arthritis. *Scand J Rheumatol;* 44:106–110.

[15] Henchoz Y, Bastardot F, Guessous I, et al., (2021), Physical activity and energy expenditure in rheumatoid arthritis patients and matched controls. *Rheumatology*; 51:1500–1507.

[16] Ölçer G, Dağ A, Kaşlı K, et al., (2020), Physical activity and exercise in patients with rheumatism in the COVID-19 Pandemic. *Türkiye Klinikleri*; 1:69–74

[17] Lee PH, Macfarlane DJ, Lam TH, et al., (2011), Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *Int J Behav Nutr Phys Act.;* 8:115.

[18] Song JE, Chae HJ, Kim CH. (2014), Changes in perceived health status, physical symtoms, and sleep satisfaction of postpartum women over time. *Nursing and Health Sciences;* 16:335–342.

[19] Nicklin J, Cramp F, Kirwan J, et al., (2010), Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. *Arthritis Care Res;* 62:1559–1568.

[20] Asheghvatan, A. and Arjmand, A. (2025). A Systematic Review of Postoperative Pain Management with Ketorolac in Patients Undergoing Laparoscopic Cholecystectomy. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(8), 257-265.

[21] Samimi, A. (2025). Assessment of Risks Arising from Neuropsychological Crises in Cardiac Patients Using FMEA. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research,* 1(7), 196-203.

[22] Milanifard, M. and Hashemloo, A. (2025). Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(7), 204-212.

[23] Henchoz Y, Zufferey P, So A. (2013), Stages of change, barriers, benefits, and preferences for exercise in RA patients: a cross- sectional study. *Scand J Rheumatol;* 42:136–145.

[24] Gümüş Y, Kitiş Y. (2015), The validity and reliability of exercise behavior change Scales. *Journal of Hacettepe University Faculty of Nursing;* 2:1–19.

[25] Zhang SX, Wang Y, Rauch A, et al., (2020), Unprecedented disruption of lives and work: health, distress and life satisfaction of working adults in China one month into the COVID-19 outbreak. *Psychiatry Res;* 288:112958.

[26] Guo YR, Cao QD, Hong ZS, et al., (2020), The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res;* 7:11

[27] Sveaas SH, Smedslund G, Hagen KB et al., (2017), Effect of cardiorespiratory and strength exercises on disease activity in patients with inflammatory rheumatic diseases: a systematic review and meta-analysis. *Br J Sports Med;* 51:1065– 1072.

[28] Hernández-Hernández V, Ferraz-Amaro I, Díaz- González F. (2014), Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology (Oxford);* 53:722– 731.

[29] Swinnen TW, Scheers T, Lefevre J, et al., (2014), Physical activity assessment in patients with axial spondyloarthritis compared to healthy controls: a technology-based approach. *PLoS One;* 9: e85309.

[30] Makay B, Kiliçaslan SK, Anik A, et al., (2017), Assessment of sleep problems in children with familial Mediterranean fever. *Int J Rheum Dis.;* 20:2106–2112.

[31] Chaput JP, Dutil C, Sampasa-Kanyinga H. (2018), Sleeping hours: what is the ideal number and how does age impact this. *Nat Sci Sleep;* 10:421–430.

[32] Duruoz MT, Unal C, Bingul DK, et al., (2018), Fatigue in familial Mediterranean fever and its relations with other clinical parameters. *Rheumatol Int;* 38:75–81