

ORIGINAL ARTICLE

Skeletal Muscle Mass, Muscle Strength, and Quality of Life in Adult Patients with Familial Mediterranean Fever: A Comparative Study with Healthy Controls

Erişkin Ailevi Akdeniz Ateşi Hastalarında İskelet Kası Kütlesi, Kas Kuvveti ve Yaşam Kalitesi: Sağlıklı Kontrollerle Karşılaştırmalı Bir Çalışma

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ABSTRACT

Aim: This study (1) compared skeletal muscle mass (SMM) and muscle strength in familial Mediterranean fever (FMF) patients with those of healthy controls (HCs) and (2) investigated the association of SMM and muscle strength with disease severity and quality of life (QOL).

Materials and Methods: This study included 31 FMF patients and 30 matched HCs. Disease severity was evaluated using the International Severity Scoring System for FMF (ISSF). Body composition parameters were measured using a bioelectrical impedance analysis. Grip and pinch strengths were calculated for muscle strength. Health status was assessed with Short Form 36 (SF-36).

Results: The all-body composition parameters of the FMF patients, including SMM, were similar to those of the HCs, with significantly lower grip and pinch strengths. All SF-36 scores of the FMF patients were significantly lower than those of the HCs. Positive correlations were observed between muscle-related indices and pinch strength for some SF-36 domains.

Conclusion: Muscle- or fat-related indices were similar among adult patients with FMF and the HCs. In contrast, patients with FMF had a poorer health-related QOL and lower grip and pinch strengths than the HCs. Further studies are needed to determine the clinical significance of these correlations in patients with FMF.

Keywords: Familial Mediterranean fever, skeletal muscle, muscle strength, quality of life

ÖZ

Amaç: Bu çalışmanın amacı, (1) erişkin ailevi Akdeniz ateşi (AAA) hastalarında iskelet kası kütlesi (İKK) ve kas kuvvetini sağlıklı kontrollerle (SK) karşılaştırmak ve (2) İKK ve kas kuvveti ile hastalık şiddeti ve yaşam kalitesi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Çalışmaya 31 AAA hastası ve eşleştirilmiş 30 SK dâhil edildi. Hastalık şiddeti, AAA için uluslararası şiddet skorlama sistemi (ISSF) kullanılarak değerlendirildi. Vücut kompozisyon parametreleri, biyoelektrik impedans analizi (BİA) kullanılarak ölçüldü. Kas kuvveti için el kavrama ve parmak kavrama kuvvetleri değerlendirildi. Yaşam kalitesi, Kısa Form-36 (KF-36) kullanılarak değerlendirildi.

Bulgular: AAA hastalarının İKK dâhil tüm vücut kompozisyon parametreleri SK grubu ile benzer, el kavrama ve parmak kavrama kuvvetleri ise istatistiksel olarak anlamlı düşüktü. AAA hastalarının tüm KF-36 skorları SK grubundan anlamlı düşüktü. Kasla ilgili indeksler ve parmak kavrama kuvveti ile bazı KF-36 skorları arasında pozitif korelasyonlar bulundu.

Sonuç: Bu çalışma, erişkin AAA hastalarında BİA ile ölçülen kas veya yağ ile ilişkili indekslerin SK grubu ile benzer olduğunu göstermiştir. Buna karşılık, AAA hastalarında sağlıklı ile ilgili yaşam kalitesi ve el kavrama ve parmak kavrama kuvvetleri SK grubundan daha düşüktü. FMF hastalarında bu korelasyonların klinik önemini belirlemek için ise daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ailevi Akdeniz ateşi, iskelet kası, kas kuvveti, yaşam kalitesi

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease among all hereditary periodic fever syndromes. Certain ethnic groups in the Mediterranean region, including Turks, experience the devastating effects of the disease (1). Patients typically experience the brief and recurrent episodes of fever and serositis. Appropriate management of the disease with early diagnosis prevents the development of amyloid A (AA) amyloidosis, which is the main cause of death in FMF patients (2). In FMF, the mutated form of pyrin, which is derived from pathological variants in the MEFV gene, activates caspase-1, stimulating the production of interleukin (IL)-1 β and IL-18, which are some of the most potent proinflammatory cytokines, and subsequently a series of inflammatory pathways

are triggered (3). In addition to these cytokines, there is an increase in IL-6 and tumor necrosis factor (TNF)- α . (4). Beyond the typical muscle involvement of FMF, these inflammatory mediators, which can be higher concentrations in the attack-free period, may also be associated with skeletal muscle loss and dysfunction in patients (5, 6). Indeed, the results of a study by Durmaz et al. (7) indicated a significant association between cachexia, which is characterized by skeletal muscle loss, and FMF in females. However, that study has some important methodological limitations, and its findings cannot be generalized. Therefore, there is a need for additional information about the body composition, skeletal muscle mass (SMM), and muscle strength of patients with FMF.

The aim of this exploratory study was to determine (1) whether SMM and muscle strength, as measured by validated devices, were lower in patients with FMF than in matched healthy controls (HCs) and (2) whether SMM and muscle strength were associated with disease severity and quality of life (QOL).

Materials and Methods

Study Design

This cross-sectional, case-control study was conducted in the rheumatology clinics of a tertiary care university hospital between July 2021 and December 2022. The study protocol was approved by the local ethics committee (date: 23.06.2021 and approval number: 2021/448). The study complied with the principles of the Helsinki Declaration on good clinical practice. All participants were informed about the study, and their written informed consent was obtained.

Study Participants

The study comprised 31 FMF patients (8 male, 23 female) meeting the Tel-Hashomer criteria for clinical diagnosis and 30 HCs (11 male, 19 female) aged 18 and 65 years (8). Patients who had an attack within the last 2 weeks, had neurologic, psychiatric, thyroid or malignant disease, hypertension, or diabetes mellitus, had any rheumatic disease diagnosis in addition to FMF, or had any problem involving the musculoskeletal system, including congenital, traumatic or surgical problems, were excluded. Age- and sex-matched healthy participants with no history of systemic disease, medication use, musculoskeletal complaints, or trauma and no family history of FMF were included as the control group. Age, gender, smoking and alcohol use, and dominant extremity of each participant were questioned. In addition, disease-related data of FMF patients, including disease duration, disease progression, duration of colchicine use, and total daily dose of colchicine, were collected. Detailed musculoskeletal, neurological, and manual muscle strength examinations were also performed.

Measures

Disease severity was assessed using the International Severity Scoring System for FMF (ISSF). This scoring system developed by Demirkaya et al. (9) is evaluated with a total of 10 points over 9 parameters. A score of 2 and below indicates mild disease, a score of 3-5 points indicates moderate disease and a score of 6 or more points indicates severe disease.

Body height was measured in a stretched position with a portable stadiometer with an accuracy of 1 mm. Other body composition parameters were measured using a multifrequency bioelectrical impedance analysis (BIA) method. The Inbody 270 device (Biospace, Seoul, Korea) was selected for BIA. Each participant's body mass, body fat mass (BFM), fat-free mass (FFM), SMM, appendicular SMM (ASMM), trunk muscle mass (TMM), body mass index (BMI), skeletal muscle index (SMI), body fat percentage (BFP) and fat-free mass index (FFMI) were calculated and recorded (10). For body composition analysis, the Inbody 270 device has been shown to be valid and reliable (11).

Muscle strength was assessed by grip and pinch strengths of the dominant extremity. Participants were given a visual demonstration of the techniques with standardized verbal instructions describing how to perform the test. Grip strength was measured using a calibrated hydraulic hand dynamometer (Jamar® Hydraulic Hand Dynamometer) in the standard position recommended by the American Society of Hand Therapists (12). Participants were seated on a chair without arm support, and measurements were taken of the shoulder in adduction and neutral rotation of the elbow at 90 degrees of flexion, and of the forearm and wrist in the neutral position. Key pinch strength was assessed using a calibrated pinch gauge (Baseline® Hydraulic Pinch Gauges). Participants were seated on a chair with the shoulders in adduction and neutral rotation, with the elbows flexed at 90°, forearm in the neutral position, and with the wrists dorsiflexed at 0° to 30° and ulnar deviated at 0° to 15° (13). To reduce the effect of fatigue on all measurements, one minute was allowed between each measurement. The participants performed three trials each for the grip strength measurement and pinch strength measurement. The values used in this study represent the highest value obtained from the three measurements.

Health status was assessed using the Short Form 36 (SF-36) health survey questionnaire. SF-36 consists of 36 items related to eight health scales: physical functioning, social functioning, physical role limitation, emotional role limitation, mental health, vitality, bodily pain, and general health perception. The two basic dimensions of health, physical and mental, are derived from these eight scales. Higher scores indicate a better QOL. The Turkish validity and reliability study of the scale was conducted by Koçyiğit et al (14) in 1999.

Statistical Methods

Data analysis was performed using IBM SPSS Statistics version 22.0 software (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used to test whether the assumption of normal distribution was fulfilled. Categorical data were expressed as numbers (n) and percentages (%), while quantitative data were expressed as mean \pm standard deviation (SD). The Student's t-test or Mann-Whitney U test was utilized to compare age, body composition parameters, muscle strength, and SF-36 scores between the patient and control groups, depending on the distribution of the variables. In the patient group, the relationship between body composition parameters, muscle strength, disease severity, and QOL was evaluated with Spearman's correlation coefficient. A p-value less than 0.05 was considered statistically significant.

Results

In total, 61 individuals (31 FMF patients, 30 HCs) were added in this study. There were no statistically significant differences in the demographic characteristics between the groups (Table 1).

The duration of disease and the duration of colchicine use in the FMF patients were 10.9 ± 6.0 years and 8.0 ± 4.7 years, respectively. The mean colchicine dose of

the patients was 1.3 ± 0.5 mg/day. None of the patients used biological agents. The mean ISSF score was 1.42 ± 0.96 . According to the ISSF score, 27 patients had mild disease and four patients had moderate disease.

There were no statistically differences between FMF patients and HCs in terms of body composition parameters. However, the grip strength and pinch strength of FMF patients were significantly lower than those of HCs ($p = 0.045$ and $p = 0.009$, respectively) (Table 2).

Consistent with low level of QOL in FMF patients, all eight domains of the SF-36 score were significantly lower than the HCs (Table 3).

The strength of the associations among body composition parameters, muscle strength, disease severity, and QOL was investigated using Spearman's rank correlation in FMF patients (Table 4). The SF-36 physical component summary (PCS) showed weak to moderate correlations with SMM, FFM, SMI, FFMI and ASMM. In addition, there was a moderate correlation between SF-36 PCS and pinch strength, and a weak correlation between SF-36 mental component summary (MCS) and pinch strength. No significant correlation was found between ISSF and body composition parameters or grip and pinch strength.

Table 1. Demographic characteristics of the FMF patients and HCs.

| | FMF (n=31) | HCs (n=30) | p-value |
|---------------------------|-----------------|-----------------|--------------------------|
| Age, years | 37.7 ± 11.0 | 35.0 ± 9.7 | 0.305[†] |
| Gender, female | 23 (74.2) | 19 (63.3) | 0.360[‡] |
| Body weight, kg | 71.0 ± 12.7 | 70.8 ± 14.4 | 0.959[†] |
| Height, m | 1.63 ± 0.1 | 1.68 ± 0.1 | 0.720[†] |
| BMI, kg/m ² | 26.6 ± 4.6 | 25.0 ± 3.9 | 0.132[†] |
| Smoking | 11 (35.5) | 9 (30.0) | 0.648[‡] |
| Alcohol use | 2 (6.5) | 1 (3.3) | 1.000[*] |
| Dominant extremity, right | 28 (90.3) | 28 (93.3) | 1.000[*] |

Abbreviations: BMI, body mass index.
Data were expressed as mean \pm standard deviation for continuous variables and as numbers and percentages for categorical variables.
[†]Independent samples t-test, [‡]Chi-square test, ^{*}Fisher's exact test

Table 2. Comparison of body composition parameters and muscle strength between the FMF patients and the HCs.

| | FMF (n=31) | HCs (n=30) | p-value |
|-------------------------|-----------------|-----------------|--------------------------|
| SMM, kg | 26.3 ± 5.8 | 27.8 ± 7.9 | 0.379[†] |
| BFM, kg | 23.8 ± 8.5 | 20.6 ± 7.4 | 0.127[‡] |
| PBF, % | 33.0 ± 8.6 | 29.0 ± 7.9 | 0.065[‡] |
| FFM, kg | 47.3 ± 9.5 | 50.3 ± 11.5 | 0.367[†] |
| SMI, kg/m ² | 7.3 ± 1.1 | 7.2 ± 1.1 | 0.930[†] |
| FFMI, kg/m ² | 17.7 ± 2.1 | 17.6 ± 2.4 | 0.804[†] |
| TMM, kg | 20.8 ± 5.1 | 21.9 ± 5.0 | 0.329[†] |
| ASMM, kg | 19.6 ± 4.8 | 20.8 ± 5.6 | 0.417[†] |
| Right arm, kg | 2.6 ± 0.8 | 2.6 ± 0.8 | 0.989[†] |
| Left arm, kg | 2.6 ± 0.8 | 2.6 ± 0.8 | 0.976[†] |
| Right leg, kg | 7.3 ± 1.6 | 7.8 ± 2.0 | 0.330[†] |
| Left leg, kg | 7.2 ± 1.7 | 7.8 ± 2.0 | 0.273[†] |
| Grip strength, kg | 30.5 ± 14.0 | 35.7 ± 12.4 | 0.045[†] |
| Pinch strength, kg | 7.2 ± 2.5 | 8.6 ± 2.2 | 0.009[†] |

Abbreviations: SMM, skeletal muscle mass; BFM, body fat mass; PBF, percent of body fat; FFM, fat free mass; SMI, skeletal muscle index, FFMI, fat free mass index; ASMM, appendicular skeletal muscle mass; TMM, trunk muscle mass.
Data were expressed as mean \pm standard deviation for continuous variables.
Bold values show statistical significance.
[†]Mann-Whitney U Test, [‡]Independent samples t-test

Table 3. Comparison of the health-related QOL between FMF patients and HCs.

| | FMF (n=31) | HCs (n=30) | p-value |
|---------------------------|-----------------|-----------------|------------------------------|
| SF-36 PCS | 70.5 ± 21.6 | 93.8 ± 5.6 | <0.001[†] |
| SF-36-MCS | 69.2 ± 19.1 | 84.2 ± 11.6 | <0.001[†] |
| SF-36 domains | | | |
| Physical functioning | 81.1 ± 20.0 | 97.8 ± 7.2 | <0.001[†] |
| Physical role limitation | 72.6 ± 43.0 | 100.0 ± 0.0 | 0.001[†] |
| Bodily pain | 77.1 ± 27.1 | 94.0 ± 8.3 | 0.016[†] |
| General health | 51.0 ± 25.8 | 83.5 ± 15.1 | <0.001[†] |
| Vitality | 44.5 ± 19.4 | 65.9 ± 15.7 | <0.001[†] |
| Social functioning | 85.5 ± 20.7 | 96.6 ± 12.5 | 0.003[†] |
| Emotional role limitation | 79.6 ± 40.1 | 97.7 ± 12.4 | 0.026[†] |
| Mental health | 67.2 ± 18.8 | 77.0 ± 13.8 | 0.035[†] |

Abbreviations: PCS, physical component summary; MCS, mental component summary.
Data were expressed as mean \pm standard deviation.
Bold values show statistical significance.
[†]Mann-Whitney U Test.

Table 4. Correlation of FMF patients' body composition parameters and grip strength and pinch strength with disease severity and QOL.

| | ISSF | | SF-36 PCS | | SF-36 MCS | |
|----------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|----------------------|
| | Correlation coefficient | p-value [†] | Correlation coefficient | p-value [†] | Correlation coefficient | p-value [†] |
| BMI | -0.143 | 0.444 | 0.189 | 0.308 | 0.127 | 0.495 |
| SMM | -0.246 | 0.190 | 0.433 | 0.017 | 0.300 | 0.108 |
| FFM | -0.263 | 0.161 | 0.450 | 0.013 | 0.312 | 0.093 |
| SMI | -0.185 | 0.320 | 0.459 | 0.009 | 0.251 | 0.172 |
| FFMI | -0.258 | 0.169 | 0.540 | 0.002 | 0.338 | 0.068 |
| TMM | -0.165 | 0.374 | 0.268 | 0.145 | 0.052 | 0.783 |
| ASMM | -0.168 | 0.368 | 0.394 | 0.028 | 0.238 | 0.198 |
| Grip strength | -0.078 | 0.677 | 0.330 | 0.069 | 0.181 | 0.329 |
| Pinch strength | -0.314 | 0.085 | 0.632 | <0.001 | 0.383 | 0.033 |

Abbreviations: ISSF, international severity scoring system for familial Mediterranean fever; PCS, physical component summary; MCS, mental component summary; BMI, body mass index; SMM, skeletal muscle mass; FFM, fat free mass; SMI, skeletal muscle index; FFMI, fat free mass index; TMM, trunk muscle mass; ASMM, appendicular skeletal muscle mass.
[†]Spearman correlation test.

Discussion

This study focused on the differences in SMM and other body composition characteristics between patients with adult FMF and matched HCs. We also investigated the relationships between muscle-related parameters and muscle strength with disease severity and health-related QOL. Our results revealed that body composition parameters of FMF patients were comparable to HCs, while grip strength and pinch strength were lower than them.

To the best of our knowledge, this is the first study to evaluate in detail the differences in body composition characteristics between HCs and patients with FMF. In a study by Sari et al. (15), some body composition parameters measured by BIA in patients with FMF and HCs were compared and BMI, BFM, PBF and FFM values were found similar between the two groups. Similarly, in our study, BMI, FFM and all measures of body fat were similar between patients with FMF and HCs. Collectively, muscle- or fat-related indices do not appear to be affected in the body composition of patients with FMF. Conversely, the prevalence of cachexia in female patients with FMF was 27.5%, which was significantly higher than that in HCs, in

another study by Durmaz et al. (7). In the same study, body weight, BMI and SMM were also found lower in female patients with FMF than in HCs. The different results in the study by Durmaz et al. (7) may be related to differences in study methodology, such as the inclusion of relatively younger female patients with severe disease. Therefore, it was not possible to directly compare the results of this study with our results.

Some forms of cachexia are associated with diseases in which inflammation of the tissues and a higher pro-inflammatory state are the main triggers of the progressive loss of muscle mass. These elevated levels of pro-inflammatory mediators, including TNF- α , IL-1 and IL-6, cause skeletal muscle wasting by disrupting the balance in the body toward protein degradation through various molecular pathways (16). Therefore, there is evidence that body composition is profoundly affected in chronic autoimmune and inflammatory conditions (17). A typical example of such condition is the form of cachexia that occurs in rheumatoid arthritis (RA) with a frequency of 15 to 32%, known as rheumatoid cachexia. In this meta-analysis, possibly because the majority of patients included had moderate to high disease activity, no association was found between disease activity and rheumatoid cachexia in RA (18). However, Hufman et al. (19) also showed muscle concentrations of inflammatory markers correlated with disease activity, disability, pain, and physical inactivity in patients with RA. Our results suggest that body composition parameters, including muscle related indices, are not affected in FMF, which is a chronic autoinflammatory disease. One of the main reasons for this finding may be that proinflammatory cytokine concentrations, which increase during the acute attack period and decrease or return to normal during the attack-free period, do not lead to ongoing excessive protein degradation associated with muscle wasting. Another reason for this finding may be the mild disease severity of the majority of the FMF patients who were included in our study. In a study of FMF patients with persistent inflammation, 93.7% had moderate to severe disease according to the ISSF (20). Therefore, body composition characteristics may be affected in patients with FMF who have moderate to severe disease.

Another finding of our study was that the grip strength and pinch strength were significantly lower in patients with FMF compared with HCs. Interestingly, pinch strength was positively correlated with SF-36 PCS and MCS scores whereas grip strength was not associated with either. On the other hand, in previous studies conducted in patients with FMF, grip strength was similar to the controls, while strength in other muscle groups, including hip flexors, extensors and abductors, knee flexors and extensors, and ankle dorsiflexors, was lower in HCs (7, 21). In another study, patients with FMF aged 8-18 years had significantly lower quadriceps muscle strength than the controls. This finding was associated with decreased functional capacity as measured by the 6-min walk test (22). To the best of our knowledge, pinch strength has not been

previously evaluated in patients with FMF. According to our results, the difference in pinch strength between patients with FMF and HCs appears to be greater than that of the grip strength. Pinch strength is one of the physical performance assessment methods that can be practically and easily measured in outpatient clinic conditions and is known as precise grip (23). Further studies are needed to investigate the clinical significance of the decline in pinch strength in patients with FMF, especially in relation to limb muscle strengths and physical activity.

The relationship between the dose and duration of colchicine used and body composition parameters or muscle strength was not evaluated in the study. It is known that neuropathy and/or myopathy can rarely develop during colchicine therapy. A recent systematic review has shown that in most cases, signs of both neuropathy and myopathy coexist, but myopathy is predominant. In addition, 82% of the reported cases had a significant comorbidity and/or possible drug interaction potentially associated with colchicine-induced neuromyopathy (24). Patients with evidence of neuromyopathy or neuromyopathy-related comorbidities were not included in this study anyway. Therefore, we believe that the use of colchicine did not have a major effect on the results of the study.

In this study, all domains of the SF-36 score used to evaluate health-related QOL were also significantly lower in the patient group than in the HCs. In addition, a correlation was found between SF-36 PCS score and SMM, FFM, SMI, FFMI, and ASMM. In contrast, there was no significant association between QOL and muscle-related indices in HCs (data not shown). It was a common finding that QOL-related domains (for SF-36) were lower than in the HCs, even in FMF patients with mild disease severity (25). Unlike other studies, Durmaz et al. (7) showed that female patients with FMF who had cachexia had a significantly lower QOL than those without cachexia. Similarly, Fukuda et al. (26) also demonstrated that a decrease in BMI due to muscular loss was associated with a lower QOL in patients with RA. On the other hand, Kim et al. (27) reported no decrease in SMM in patients with ankylosing spondylitis compared with the controls and no association with QOL. In our study, we also found no significant difference in muscle-related indices in FMF patients versus the HCs. These findings also confirm that muscle strength is distinct from muscle mass and suggest that an individualized approach is needed to improve patients' QOL (28).

This study has several limitations. First, because of the cross-sectional study design, a prospective longitudinal study is required. Second, 87.1% of the patients with FMF included in the study had mild disease severity. Therefore, we could not examine the relationship between moderate to severe disease severity and body composition characteristics. Third, we did not assess the physical activity level of the study participants. The differences in physical activity levels between the patients and the HCs may also

have affected the muscle mass in different ways.

Conclusion

This study showed that muscle- or fat-related indices measured by BIA were similar in adult patients with FMF compared with the HCs. In contrast, patients with FMF had poorer health-related QOL as well as lower grip strength and pinch strength. Some correlations were detected among muscle-related indices, pinch grip and QOL. However, further studies are required to evaluate the clinical significance of these correlations.

Conflict of Interest

The authors have no conflict of interest with any institution or company.

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Author Contributions

Concept and design: İ.C., A.S.Ş., R.Y., S.K.K., Data Collection: R.Y., S.K.K., T.F.Ç., M.K., E.O.K., Analysis: İ.C., E.V., H.K., A.S.Ş., Writing: İ.C., S.K.K., R.Y., E.V., H.K., Critical Review: A.S.Ş., M.K., E.O.K.

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