Investigating the lower extremity–related anaerobic exercise capacity and functional status in adult patients with familial Mediterranean fever

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ABSTRACT

Objectives: No studies examined the lower extremity–related anaerobic exercise capacity or functional status in adult patients with FMF.

Methods: Twenty-four patients with FMF (12 males) and 24 age–sex-matched healthy controls (13 males) were included in the study. Lower extremity–related anaerobic exercise capacity was assessed by using Wingate Anaerobic Test. Lower extremity–related functional status was examined by using 9-Step Stair Climb Test, 10-Repetition Chair Stand Test, and Six-Minute Walk Distances. Muscle strength of hip flexors, hip extensors, knee flexors, and knee extensors were evaluated by using a hand-held dynamometer.

Results: Patients with FMF had significantly poorer results in all anaerobic exercise capacity parameters and functional status assessments (P < 0.05), except muscle strength measurements (P > 0.05). Both average and peak anaerobic exercise capacities correlated significantly with all muscle strength measurements, 9-Step Stair Climb Test, 10-Repetition Chair Stand Test times, and Six-Minute Walk Distances (P < 0.05) in patients with FMF.

Conclusion: Lower extremity–related anaerobic exercise capacity and functional status seem to be diminished in adult patients with FMF. Evaluating these parameters may be beneficial for planning more appropriate and individualized treatment regimens such as patient education and exercise counselling for patients with FMF.

KEYWORDS: Familial Mediterranean fever; exercise capacity; functional status

Introduction

Familial Mediterranean fever (FMF) is an auto-inflammatory disease due to the mutation of the Mediterranean fever (MEFV) gene. FMF is commonly seen in the Mediterranean basin [1]; however, cases with FMF are reported in the other regions of the world such as Japan, Germany, and China [2–4]. The symptoms are commonly observed in the earlier years of life, and initial attacks occur before the age of 20 years in 90% of the patients [5]. The disease is characterized by acute self-limiting inflammatory attacks of serous membranes. Attacks and remissions are observed in the course of the disease, and patients are described asymptomatic between attacks. Musculoskeletal symptoms such as arthritis of lower extremities, exercise-induced leg pain, and protracted febrile myalgia are also common [6]. These symptoms may lead to impaired physical functions, including reduced exercise capacity, diminished muscle strength, and decreased walking capabilities [7].

Exercise capacity is the ability to perform and sustain different daily activities and is investigated in two categories as aerobic (the ability of maintaining low-paced long-duration activities such as swimming) and anaerobic (the ability of performing quick and explosive tasks such as stair climbing and brisk walking). Anaerobic exercise capacity was shown to be impaired in many different chronic inflammatory diseases such as juvenile idiopathic arthritis [8, 9] and juvenile-onset idiopathic inflammatory myositis [10]. Recently, decreased anaerobic capacity was also reported in children with FMF [11].

It is well known that functional status is impaired in chronic inflammatory diseases due to chronic inflammation, fear of movement, and decreased muscle strength [12, 13]. However, the data related to physical functions of FMF patients are scarce and mainly focused on childhood period. To the best of our knowledge, only Alayli et al. investigated the walking capacity and quadriceps muscle strength in
children with FMF. These authors reported that children with FMF showed poorer results compared to healthy peers [7].

As the symptoms of FMF are usually seen in childhood, available studies related to anaerobic exercise capacity and physical functions are commonly performed in children with FMF. However, it might be important to evaluate the possible detrimental effects of an early-onset chronic disease on exercise capacity and physical functions in adulthood. Therefore, the aim of the present study was to compare the anaerobic exercise capacity and lower extremity functionality between adult patients with FMF and healthy controls and to assess the relationship between anaerobic exercise capacity and lower extremity functionality in patients with FMF.

Materials and methods
Participants
Adult patients with FMF (18–65 years) who were diagnosed according to Tel-Hashomer criteria [14] and age- and sex-matched healthy controls were invited to participate in the study. The exclusion criteria were an acute FMF attack; any problems related to neurologic, cardiac, and/or musculoskeletal systems (except arthritis); any surgery/trauma history of lower extremities; and unwillingness to participate in the study. All the participants gave written informed consents prior to participating in the study. The ethical approval was obtained from the Izmir Katip Celebi University ethics committee (number 88/2020).

Procedure
All the assessments were completed at the same day for a participant. Firstly, the physical and disease-related characteristics of the participants were recorded. Then, to eliminate the risk of fatigue, Wingate Anaerobic Test was performed. Following Wingate Anaerobic Test, 15 minutes of resting was provided, and 9-Step Stair Climb Test, 10-Repetition Chair Stand Test, and Six-Minute Walking Distance were evaluated in a random order. Fifteen minutes of rest was provided between each assessment. Patients with FMF were phoned in the following day to evaluate the development of the leg pain by using the Numeric Rating Scale (NRS) 0–10, where 0 represented no pain and 10 represented the worst imaginable pain [15].

Outcome measures
Physical and disease-related characteristics
Physical characteristics (age, sex, height, weight, and body mass index (BMI) of all participants and disease-related characteristics (time since the onset of the symptoms, time since the diagnosis, colchicine dose, MEFV mutation analysis, biological usage, and cumulative symptom history) of patients with FMF were recorded by using a standardized form.

Lower extremity–related anaerobic exercise capacity
Wingate Anaerobic Test was employed to measure the lower extremity anaerobic exercise capacity (Ergomedic 894E; Monark, Vansbro, Sweden). The test provided average and peak power by measuring the ability of cycling against a stable load for 30 seconds. The participant warmed up for 5 minutes by cycling against a minimal load before the test. Then, the participant was asked to accelerate, and when he/she reached 105 revolutions per minute, a load of 7.5% of the participant’s body weight was applied automatically by the Wingate Anaerobic Test system. The participants were encouraged verbally to complete 30 seconds throughout the test [16].

Lower extremity–related functional status
Lower extremity muscle strength. The muscle strength of hip flexors, hip extensors, knee flexors, and knee extensors was measured by using a hand-held dynamometer (Lafayette; Indianapolis, USA). The brake method was used, and the measurements were performed in standard positions [17]. The test was repeated three times by providing 2-minute rests between attempts, and the average values were recorded. Then, the values related to right and left sides were summed and divided by 2 to obtain a total score for each muscle group.

9-Step Stair Climb Test. The 9-Step Stair Climb Test was used to evaluate the anaerobic power of lower extremities functionally. The participant was instructed to ascend and descend nine steps (a height of one step was 16 cm) without using handrails. A trial was performed prior to actual testing. Then, a 10-minute rest was provided. The total time for ascending and descending nine steps was recorded in seconds [18, 19].

10-Repetition Chair Stand Test. The 10-Repetition Chair Stand Test was another functional evaluation of anaerobic power of the lower body. A standard armless chair (height: 42 cm) was used for the test. The participant was asked to rapidly perform 10 stand-ups from the chair to a fully extended standing position with his/her arms crossed on his/her chest. The timing was started when the participant’s buttocks left the chair and was stopped when they touched back to the chair for the 10th time. The time was recorded in seconds [18, 20]. A trial was allowed prior to actual testing and a 2-minute rest was provided after the trial.

Six-Minute Walking Distance. Six-Minute Walking Distance was used to assess walking ability. A 30-m flat corridor was used. The participant was asked to cover as much as distance as he/she can do without running for 6 minutes. Standard encouragement words (keep going/you are doing well) were used at 1-minute intervals. Resting was allowed during the test, but the time was not stopped in case of resting. The total distance after 6 minutes was recorded in meters [18, 21].

Statistical analysis
Statistical analysis was performed using SPSS 15 software. Shapiro–Wilk test and histograms were used to evaluate the distribution of the data. As the parametric conditions were not met, data were presented as median and interquartile ranges (IQR 25–75). The chi-square test was used to define categorical differences (biological gender) between groups. Mann–Whitney U test was used to compare the groups. Spearman’s rank-order correlation was employed to determine the relationships between the anaerobic exercise capacity and the lower extremity–related lower extremity functional status. \( P < 0.05 \) was considered as statistically significant.

Results
The study was completed with 24 patients with FMF (12 males) and 24 healthy controls (13 males). The demographic and physical characteristics of both groups and disease-related
features of patients with FMF were presented in Table 1. No significant differences were detected between groups regarding physical characteristics \( (P > 0.05) \). Two patients with FMF (8%) were using biological agents (one anakinra and one canakinumab). Seventeen patients had an analysis for MEFV mutation, and six (35%) patients were M694V homozygote.

No adverse effects were detected during or after the assessments; however, 11 (45.8%) patients with FMF described leg pain >2 (median: 4 (IQR 25/75: 4/7)) on the NRS on the following day.

Significant differences were observed between groups in all anaerobic exercise capacity parameters in favour of the control group \( (P < 0.05) \) (Table 2). Regarding lower extremity–related functional status, while no statistically significant differences were observed between groups in terms of muscle strength \( (P > 0.05) \), six-minute walking distance, chair stand test time, and stair climb test time was better in the control group \( (P < 0.05) \) (Table 3).

Both average and peak anaerobic powers (normalized to body weight) were correlated significantly with all lower extremity–related functional status scores \( (P < 0.05) \) (Table 4).

**Discussion**

According to our results, it is observed that lower extremity–related anaerobic exercise capacity and functional status were diminished in adult patients with FMF compared to their healthy peers.

As the symptoms of the FMF appear mostly in childhood, most of the investigations were conducted for this age group. On the other hand, FMF is a chronic disease, and studying the functional status in adulthood might also be crucial. Adults have important responsibilities such as working to maintain a regular income and performing house chores. These tasks commonly demand physical performance; thus, having an adequate functional status is essential. Patients with FMF mainly experience lower extremity–related problems; therefore, lower extremity–related anaerobic capacity and functional status were investigated in the present study.

The decreased anaerobic exercise capacity and functional status were reported in other inflammatory diseases previously [8–10]. Moreover, we recently demonstrated the decrease in lower extremity–related anaerobic capacity in children with FMF [11]. Alayli et al. assessed walking capacity (Six-Minute Walking Distance) and quadriceps muscle strength (hand-held dynamometer) in children with FMF [7]. They found that both walking capacities and quadriceps strength decreased in those children compared to their healthy peers. Similar to these reports, lower extremity–related anaerobic exercise capacity and walking capacity were found diminished in the adult patients with FMF in the present study. On the other hand, quadriceps muscle strength as...
represented by knee extension was not different than the healthy controls. The results of the present study revealed that while the muscle strength is restored in adulthood, exercise capacity and functional status remain diminished for these apparently healthy adults.

It is well known and were also presented by our results that the anaerobic capacity and functional status are related to muscle strength; however, according to our results as the muscle strength is similar between groups, the underlying mechanism of the difference between anaerobic exercise capacity and functional status may be related to alterations in the energy metabolism of patients with FMF. Energy metabolism may be altered by performing regular exercise and physical activity [22]. Babaoglu et al. and Tore et al. demonstrated that physical activity levels of FMF patients were decreased during attacks and attack-free periods [23, 24]. However, we did not measure the physical activity levels or exercise habits of the participants in the present study. Thus, the exact mechanisms underlying diminished anaerobic capacity and reduced functional status in patients with FMF are yet to be explored in future studies.

Long-term colchicine use was reported related to myopathy and neuropathy in rare cases [25]. Moreover, the development of colchicine myopathy was reported in patients with renal failure or in patients using other medications such as statins or tacrolimus [25–27]. However, only one patient had amyloidosis in the present study, and none of the patients were using statins or tacrolimus. Moreover, the muscle strengths were similar between groups. Thus, we believe colchicine use might not be a possible reason for decreased anaerobic capacity or functional status for our patients.

Both the 9-Step Stair Climb Test and the 10-Repetition Chair Stand Test demand anaerobic energy metabolism, and these tests were moderately found related to anaerobic exercise capacity in the present study. On the other hand, the strongest relationship was observed between the anaerobic exercise capacity and 6-minute walking distance, which relatively is an indicator of aerobic exercise capacity [28]. It seems that anaerobic and aerobic capacities are both altered in patients with FMF. However, there is no evidence related to the status of aerobic exercise capacity of patients with FMF to confirm our assumption. Future studies should investigate the status of aerobic exercise capacity and related factors.

Yenokyan et al. [29] reported that physical stress and psychological stress were major factors for triggering the attacks in patients with FMF. However, according to our results, none of our patients experienced an attack following the assessment. On the other hand, Livneh et al. [14] reported that 30% of patients experience exercise-induced leg pain. In the present study, nearly half of the patients reported 2-point or higher leg pain according to the NRS in the following day. However, their leg pain resolved spontaneously in 2 days.

Our results confirmed that it is important to keep in mind that physical tests may cause a spontaneous leg pain and the patients should be informed prior to the assessment. Besides, patients with FMF may avoid physical activity due to their exercise-induced leg pain and this may result in a decrease in their anaerobic exercise capacity.

The common mutation was M694V homozygote (6 of 17, 35%) in the present study. As FMF was diagnosed in childhood, some patients could not recall their results or were not analysed for MEFV mutations. Therefore, we could not

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### Table 3. Comparison of lower extremity-related functional status between groups.

<table>
<thead>
<tr>
<th>Functional status</th>
<th>FMF group median (IQR 25/75) (n=24)</th>
<th>Control group median (IQR 25/75) (n=24)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity muscle strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total knee extension (kg)</td>
<td>28.5 (21.9/33.9)</td>
<td>29.2 (25.3/35.7)</td>
<td>0.287</td>
</tr>
<tr>
<td>Total knee flexion (kg)</td>
<td>22.0 (15.4/24.4)</td>
<td>25.5 (21.6/35.7)</td>
<td>0.076</td>
</tr>
<tr>
<td>Total hip extension (kg)</td>
<td>28.0 (18.8/35.4)</td>
<td>29.6 (26.1/39.4)</td>
<td>0.133</td>
</tr>
<tr>
<td>Total hip flexion (kg)</td>
<td>24.8 (18.8/29.3)</td>
<td>26.6 (20.6/39.9)</td>
<td>0.142</td>
</tr>
<tr>
<td>Lower extremity related functional status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-Minute Walking Distance (m)</td>
<td>597.5 (555.4/650.2)</td>
<td>669.0 (630.0/731.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>9-Step Stair Climb Test (seconds)</td>
<td>5.7 (5.0/6.4)</td>
<td>4.8 (4.4/5.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>10-Repetition Chair Stand Test (seconds)</td>
<td>16.4 (13.7/18.0)</td>
<td>12.3 (13.4/11.0)</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>

\(n<0.05\).  
* Mann–Whitney \(U\) test.

FMF: familial Mediterranean fever, IQR 25/75: interquartile range between 25th and 75th percentiles, \(n\): number, kg: kilograms.

### Table 4. Relationships between lower extremity–related anaerobic exercise capacity and functional status in patients with familial Mediterranean fever.

<table>
<thead>
<tr>
<th>Functional status</th>
<th>Peak power (watt/kg)</th>
<th>Average power (watt/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity muscle strength</td>
<td>rho = 0.586 (P=0.003^*)</td>
<td>rho = 0.556 (P=0.005^*)</td>
</tr>
<tr>
<td>Total knee extension (kg)</td>
<td>rho = 0.745 (P&lt;0.001^*)</td>
<td>rho = 0.738 (P&lt;0.001^*)</td>
</tr>
<tr>
<td>Total knee flexion (kg)</td>
<td>rho = 0.804 (P&lt;0.001^*)</td>
<td>rho = 0.797 (P&lt;0.001^*)</td>
</tr>
<tr>
<td>Total hip extension (kg)</td>
<td>rho = 0.584 (P=0.003^*)</td>
<td>rho = 0.567 (P=0.004^*)</td>
</tr>
<tr>
<td>Total hip flexion (kg)</td>
<td>rho = 0.646 (P=0.001^*)</td>
<td>rho = 0.674 (P&lt;0.001^*)</td>
</tr>
<tr>
<td>Lower extremity–related functional status</td>
<td>rho = 0.571 (P=0.004^*)</td>
<td>rho = 0.599 (P=0.002^*)</td>
</tr>
<tr>
<td>Six-Minute Walking Distance (meters)</td>
<td>rho = 0.559 (P=0.005^*)</td>
<td>rho = 0.537 (P=0.007^*)</td>
</tr>
<tr>
<td>9-Step Stair Climb Test (seconds)</td>
<td>rho = 0.664 (P=0.001^*)</td>
<td>rho = 0.674 (P&lt;0.001^*)</td>
</tr>
<tr>
<td>10-Repetition Chair Stand Test (seconds)</td>
<td>rho = 0.559 (P=0.005^*)</td>
<td>rho = 0.537 (P=0.007^*)</td>
</tr>
</tbody>
</table>

\(\rho<0.05\).  
* Spearman’s rank-order correlation.

IQR 25/75: interquartile range between 25th and 75th percentiles, \(n\): number, kg: kilograms.
evaluate the effect of genotypes on the exercise capacity. The possible effect of the mutations and disease severity on functional status may be a point of interest for further studies.

The investigated age group (working age) is the strength of the present study. Moreover, lower extremity–related anaerobic exercise capacity and functional status were documented for the first time in these patients. On the other hand, the sample was relatively small, due to the coronavirus disease-19 pandemic. Also, the exercise or physical activity habits of the participants, which may play an important role in the anaerobic exercise capacity and functional status, were not inquired. The impact of the changes in lower extremity–related anaerobic exercise capacity and functional status on quality of life and fatigue should also be investigated in future studies. In addition, aerobic exercise capacity, upper extremity–related anaerobic exercise capacity, and functional status along with the determinants of these parameters are yet to be explored for these patients. Last, but not least, the effects of different exercise programmes on these parameters should be studied in these patients.

In conclusion, the present study showed that lower extremity–related anaerobic exercise capacity and functional status are decreased in adult patients compared to healthy peers. Thus, understanding the underlying mechanisms and exerting every effort to improve the exercise capacity and functional status by implying optimal assessment/treatment programmes are important for those patients in their productive ages. Patient education programmes and/or individualized exercise/physical activity schedules may help FMF patients to achieve optimal functional status and anaerobic exercise capacity.

Conflict of interest
None declared.

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Data availability
Data is available upon request.

Ethics and consent
All the participants gave written informed consents prior to participating in the study. The ethical approval was obtained from the Izmir Katip Celebi University ethics committee (number 88/2020).

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