Lower extremity mobility limitation and impaired muscle function in women with ulcerative colitis

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Ulcerative colitis; Muscle function; Physical performance; Body composition

Abstract

Background and aim: Fatigue, weakness and musculoskeletal manifestations are associated with IBD. An impaired nutritional status and a reduced physical activity can contribute to these clinical outcomes, impacting quality of life and increasing disability. This study aims to assess muscle strength and lower limb physical performance in female UC patients, taking into consideration disease activity, body composition and habitual physical activity.

Methods: A case-control study was performed including 23 UC female outpatients and 23 age- and BMI-matched healthy women as controls. Quadriceps strength (QS), handgrip strength (HGS), physical performance based measures (five repetitions sit-up test and 4 meter gait speed test), body composition (bioelectrical impedance analysis, anthropometry), and habitual physical activity (HPA) levels were assessed.

**Author contributions:** Cyrla Zaltman was involved in study design, editing the manuscript and provided financial support for this work. Valeria B. Braulio made all statistical analyses and was involved in editing the manuscript. Rosângela Outeiral provided the collection of all human materials and made the physical evaluation. Carmen Lucia Natividade de Castro was involved in coordinating and designing of the study. Tiago Nunes made a critical review of the manuscript and was involved in writing the final draft.

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects segments of colonic and rectal mucosa in a continuous pattern. UC has an intermittent disease course with periods of exacerbated symptoms, and periods that are relatively symptom-free. The clinical presentation depends on the extent and severity of the intestinal involvement and the presence of extra-intestinal manifestations.

Even though, UC patients often complain of musculoskeletal symptoms, muscle weakness is one of the least understood extra-intestinal manifestations associated with inflammatory bowel diseases (IBD). In this regard, very few studies have investigated the involvement of peripheral muscle function in IBD patients. Most of the available data, however, show contradictory results. Geerling et al., found significant reduction in handgrip strength (HGS) in 50 UC patients compared with controls. More recently, Werkstetter et al. detected preserved HGS, but only in female UC patients. Importantly, even though upper and lower limb functions are both central components of daily living tasks, there are currently no studies evaluating the physical performance of the lower limbs in patients with UC.

The present study, therefore, aims to reassess the upper and lower limb muscle strength in patients with UC compared with age, gender and body mass index (BMI)-matched healthy individuals. In addition, performance-based measures of mobility and the overall physical activity were also evaluated.

2. Subjects and methods

2.1. Ethical considerations

The study protocol was approved by the Ethical Committee of the University Hospital of the Federal University of Rio de Janeiro (HUCFF-UFRJ), and informed consents were obtained from all subjects.

2.1.1. Study design and the studied population

A case-control study including UC female patients and BMI and age-matched healthy women was designed. Patients and controls were recruited at the gastroenterology outpatient clinic of the HUCFF-UFRJ. UC Patients had an established diagnosis by standard clinical, radiological, histological, and endoscopic criteria. The matched controls were recruited among healthy patient’s relatives and hospital staff.

All subjects were above 18 and below 65 years of age, non-smokers and had a sedentary lifestyle, which was defined as the absence of a programmed physical activity (≥30 min) on most days of the week. Patients and controls with any chronic disease (even under medical treatment), previous total colectomy or ileostomy, current pregnancy or breastfeeding, and those with muscle and joint abnormalities (which could limit the practice of physical activity) were excluded. Subjects with less than 3 years of school or those who were, for any reason, unable to read, understand, or answer questionnaires were also excluded. A complete blood analysis was performed in all subjects and the presence of hemoglobin levels below 12 g/dL was also considered an exclusion criterion. All subjects exhibited normal plasma albumin levels (4.2 ± 3.4 g/dL).

Disease activity was assessed according to the partial Mayo score. Disease location, phenotype and age of disease diagnosis were determined according to the Montreal Classification.

2.2. Body composition

Body composition was assessed using anthropometry and bioelectrical impedance analysis (BIA). Subjects were studied at least 4 h after their last meal, and had emptied their bladders before their body weight and height were recorded. BIA was undertaken with a tetrapolar bioanalyzer device (Model 310, Biodynamics Corp, Seattle, WA-USA). Measurements were undertaken as previously described. BMI was calculated as weight (kg) divided by squared height (meters). Subjects were classified as underweight (BMI < 18.50 kg/m²), normal weight (BMI = 18.50–24.99 kg/m²), overweight (BMI ≥ 25.00 kg/m²) or obese (BMI ≥ 30.00 kg/m²), according to the World Health Organization. Fat-free mass (FFM) and fat mass (FM) were calculated from the measurements of resistance made at 50 kHz using the formula provided by the instrument manufacturer. In addition, the resistance directly read from the impedance device was considered along with height, weight, and age in the obesity-specific equation published by Segal et al. The FFM index (FFMI) was derived as FFM (kg) divided by height (m) squared (kg/m²).
2.2.1. Muscle strength
Maximum non-dominant handgrip strength (HGS) was evaluated using the JAMAR hand dynamometer (Preston, Jackson, MI, USA). The subjects performed the test while sitting comfortably with the arm extended along the body. Maximal quadriceps strength (QS) was measured in the non-dominant leg with an electro-mechanic chair dynamometer (IsoTeste Kromann-Trigher, Brazil). Subjects were asked to seat upright with arms crossed in front of the chest. Velcro straps were applied tightly across the pelvis. The dynamometer lever arm connected to the strain gauge was adjusted just proximal to the malleoli. The force values were shown at a digital display. For both HGS and QS assessments, subjects performed 3 trials, and each trial was separated by a 1 minute interval. The mean force was kept. Values below 18.9 kgf were considered decreased HGS and values below 35.6 kgf were considered decreased QS according to our sex and age-matched data base (n = 120). For each measurement, the subjects were instructed by a certified physical trainer to perform a maximal isometric contraction. The trainer was responsible for the test supervision and the maintenance of motivation.

2.2.2. Assessment of physical performance
Lower-extremity functional performance was assessed by measures of ability to rise from a chair and walking velocity with the assistance of the same certified physical trainer. Both tests were measured to the nearest 0.01 s. A digital chronometer (Chronometer Kenko Sport Timer, model CR8010, Brazil) was used to measure the time spent on each of the two tests.

2.3. Sit-up test (ST)
To test the ability to rise from a chair, a straight-backed chair was placed next to a wall; participants were asked to fold their arms across their chest and to stand up from the chair one time. If successful, participants were asked to stand up and sit down five times as quickly as possible, and were timed from the initial sitting position to the final standing position at the end of the fifth stand. Values above 11.4 s indicate poor performance.

2.4. Gait speed (GS)
To test walking speed at normal pace, a test track area of 4-meter walking course with an additional 2-meter at either end was set up. Subjects were instructed to walk at a comfortable pace. Two trials were conducted. In order to avoid interference from the acceleration and deceleration phases of the gait trials, only the data obtained from 2 to 6 m were considered for statistical analysis. Results are reported as the mean of the two trials in seconds/4 m or in m/s. A value below 0.8 m/s indicates walking impairment.

2.4.1. Habitual physical activity level (HPA)
The Brazilian validated version of the Baecque questionnaire was used to evaluate the HPA level and encompasses three distinct dimensions which are physical activity at work, sport during leisure-time, and other physical activity during leisure-time excluding sport. It consists of 16 questions involving the three HPA scores related to the previous 12 months: (1) occupational physical activity, consisting of eight questions, (2) physical exercise in leisure, consisting of four questions, and (3) leisure and locomotion activities, consisting of four questions. The total score for HPA (ranging from 3 to 15 [minimum to maximum value]) is obtained by adding the three scores of the specific groupings of activities. Higher scores indicate more physically active subjects.

2.4.2. Statistical analysis
Data are presented as mean ± standard deviation (SD), number of subjects, percentage, and as odds ratio (OR) with 95% confidence intervals (95% CI). Statistical analyses were performed using Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS, Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to evaluate the normal distribution of datasets. Student’s t-test or Mann–Whitney U test compared data among subjects. Binary logistic regressions were used to study potential predictors associated with muscle strength and physical performance in the sample. Input variables were the presence of UC in the sample, age, BMI, and habitual physical activity. Multiple linear regression analysis was conducted to assess independent factors associated with muscle strength and physical performance in the UC group. Statistical significance was considered when P < 0.05.

3. Results

3.1. Clinical characteristics and body composition parameters
Table 1 shows the clinical characteristics for the UC subjects and controls. There were no significant differences in age, body composition and nutritional status between both groups. Sixty-five percent of the UC group had active disease. Of these, 93% had mild to moderate activity. A high prevalence of obesity plus overweight was found in the recruited UC subjects (61%) and only one patient was underweight (BMI = 16.9 kg/m²) and had low FFMI (13.2 kg/m²). This patient was in clinical remission.

3.2. Univariate comparison of muscle strength, physical performance tests and habitual physical activity between UC patients and controls
The results for HGS, QS, ST, GS and the HPA evaluation for UC patients and controls are summarized in Fig. 1. QS was significantly decreased in UC patients compared with controls (−6%). UC patients were significantly slower than controls at the ST (−32%) and at the GS test (−17%). In addition, HPA levels were significantly decreased in UC patients compared with controls (−30%). There was no significant difference in HGS between both groups.

3.3. Predictors for impaired muscle strength and poorer physical performance
Multivariate binary logistic regression results evaluating predictors for decreased muscle strength and impaired physical performance can be found in Table 2. In this analysis, in the total population of UC patients and controls, having the
diagnosis of UC was independently associated with a decreased QS and a slower ST. No factor was independently associated with decreased HGS and HPA was found to be protective against an impaired GS.

3.4. Multiple linear regression to assess the association between disease activity and muscle strength and physical performance in UC patients

Multivariate linear regression results in the UC group can be found in Table 3. Disease activity in this cohort was not correlated to changes in muscle strength and physical performance. In this analysis, BMI was the only factor independently correlated to any outcome (QS and ST). In this regard, for instance, holding all the other independent variables constant, a gain of one unit of BMI might lead to an average increase of 0.3 kgf in QS. In relation to the ST, BMI had the opposite effect, i.e., increases in BMI were directly associated with a slower sit-up test.

4. Discussion

The chronic systemic inflammation that takes place in UC has been previously suggested to affect the muscular performance of patients. Although no direct link between IBD-related inflammation and muscle impairment has been demonstrated, studies on other inflammatory conditions have shown that higher levels of chronic inflammation markers, including interleukin-1, interleukin-6, tumor necrosis factor-alpha or CRP are associated with decreased muscle strength, lower muscle mass, and disability. Some mechanisms have been proposed to explain the role of systemic inflammation on muscle function and limited mobility. A possible explanation could be the direct effect of increasing levels of IL-6 or TNF-α on skeletal muscle protein breakdown with simultaneous decrease in the rate of protein synthesis. Other mechanism might be the negative impact that chronic inflammation has on endothelial integrity. A loss of endothelial integrity might promote a reduction in gap junction communication impacting the coordinated vasodilator response required to increase blood flow to deliver oxygen and nutrients for muscle activity.

In the present study, UC seems to impact mobility and muscle performance, with women with UC having mild to moderate mobility limitations compared with gender, age and BMI-matched healthy controls. These patients had decreased lower limb strength with normal upper limb performance. This impairment in physical performance was evaluated by the gait speed test and the chair stand test,
two components of the Short Physical Performance Battery which is a widely used tool that measures physical performance of the lower limbs. A reduction in mobility evaluated by these measurements can detect pre-clinical limitations and predict future disability in non-disabled people. The detected alterations in physical performance suggest that UC patients might be under a higher risk to develop difficulties in the performance of common daily living activities. In line with these findings, in our cohort, UC patients had lower physical activity levels than controls, which is in agreement with previous work that found reduced physical activity in UC children and adolescent with quiescent disease.

Our results are in accordance with those of Werkstetter et al. who also observed preserved upper limb strength in female children and adolescents with mild UC with short disease duration. In contrast, Valentini et al. described reduced HGS in a group of female adults with UC in remission, but these patients had longer disease duration. Since the disease duration in our cohort was similar to the latter study, the discrepancy between results may be due to the higher prevalence of malnutrition (40%) in the study by Valentini et al. as it has been shown that grip strength is a sensitive method for detecting nutritional changes. Concerning lower limb strength, our results contradict those of Geerling et al. who showed similar QS in UC patients compared with healthy controls. In their study, however, the sample included patients with recent UC diagnosis which could indicate that muscle strength is not yet affected in early stages of the disease.

![Figure 1](https://academic.oup.com/ecco-jcc/article-abstract/8/6/529/422409)

**Figure 1** Handgrip strength (A) and quadriceps strength (B) in kilogram-force, sit-up test in seconds (C), gait velocity in meters per second (D) and the habitual physical activity score results (E) are presented in the graphics. Groups of patients are shown in different bars corresponding to controls (CON) and UC patients (UC). Statistical significance was considered when \( P < 0.05 \).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>B</th>
<th>S.E.</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>Decreased handgrip strength</td>
<td>Presence of UC</td>
<td>1.234</td>
<td>0.950</td>
<td>3.434</td>
<td>0.534 22.097</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>Age</td>
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<td>0.041</td>
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<td>0.092</td>
<td>0.256</td>
<td>1.097</td>
<td>0.663 1.813</td>
<td>0.719</td>
</tr>
<tr>
<td>Decreased quadriceps strength</td>
<td>Presence of UC</td>
<td>2.729</td>
<td>1.155</td>
<td>15.312</td>
<td>1.592 147.269</td>
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<td>0.047</td>
<td>0.989</td>
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<td>0.722 1.004</td>
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<td>Impaired sit-up test</td>
<td>Presence of UC</td>
<td>2.000</td>
<td>0.697</td>
<td>7.389</td>
<td>1.887 28.939</td>
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<td>0.041</td>
<td>1.030</td>
<td>0.950 1.117</td>
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<tr>
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<td>0.057</td>
<td>0.059</td>
<td>1.059</td>
<td>0.944 1.188</td>
<td>0.328</td>
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<tr>
<td></td>
<td>Habitual physical activity</td>
<td>0.018</td>
<td>0.229</td>
<td>1.018</td>
<td>0.651 1.594</td>
<td>0.937</td>
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<tr>
<td>Impaired gait speed</td>
<td>Presence of UC</td>
<td>1.368</td>
<td>0.861</td>
<td>3.927</td>
<td>0.726 21.225</td>
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<td>0.040</td>
<td>1.005</td>
<td>0.928 1.087</td>
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<tr>
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<td>0.243</td>
<td>0.591</td>
<td>0.392 0.890</td>
<td>0.012</td>
</tr>
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</table>
The multivariate analysis identified the diagnosis of UC and obesity as two independent factors influencing QS. These factors, however, exert different effects on muscle performance. In this regard, the presence of UC decreased muscle strength and obesity contributed to its increase. When the UC group was analyzed separately, obesity was the sole independent factor associated with QS (protection), regardless of disease activity and HPA. These findings are in line with the study by Hulens et al. who found increased QS in obese compared with lean healthy women age- and physical activity-matched. According to these authors, a plausible explanation for the stronger quadriceps muscle in obese subjects is the training effect of the weight-bearing activities. Regarding the ST, however, increased BMI led to the opposite effect, and our data show that BMI was strongly associated with different outcomes but restrict the generalization of these findings and prevent an accurate determination of the magnitude of the risk, given the large confidence intervals observed. In this regard, it is important to stress, however, that the control group was pair-matched by gender, age and BMI, controlling for the main factors impacting mobility impairment.

In conclusion, our results suggest that female UC patients have poorer lower limb performance and impaired muscle strength when compared with matched controls. An early clinical evaluation of body composition, nutritional status and physical performance of the lower limbs, therefore, may identify UC patients with a pre-clinical stage of disability who may benefit from earlier healthy lifestyle interventions, such as body weight control and a personalized exercise regimen.

Conflict of interest

No conflict of interest.

References


Table 3  Multiple linear regression to assess independent factors associated with muscle strength and physical performance results in the UC group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>R²</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Handgrip strength (kgf)</td>
<td>Disease activity</td>
<td>-1.519</td>
<td>3.170</td>
<td>-0.107</td>
<td>0.637</td>
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<td>0.177</td>
<td>0.374</td>
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<td>0.257</td>
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<td>0.853</td>
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<td>Sit-up (S)</td>
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<td>0.642</td>
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<td>Disease activity</td>
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<td>0.088</td>
<td>-0.191</td>
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