



Muscle function and quality of life in the Crohn's disease

Função muscular e qualidade de vida na Doença de Crohn

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Abstract

Introduction: Crohn's disease (CD) is an inflammatory bowel disease, marked by exacerbations and remissions periods. Peripheral manifestations in CD may be present with the syndrome of skeletal muscle dysfunction (SMD), which is characterized by loss of muscle strength, fatigue complain, limited exercise capacity and impaired quality of life of these patients. **Objective:** Evaluate muscle strength, physical capacity and quality of life of patients with CD and compare them with healthy controls. **Methods:** 18 patients CD and 12 healthy controls matched for age and sex were involved. Peripheral muscle strength evaluated by handgrip strength of the dominant hand and respiratory muscle strength by measures of respiratory muscle strength (maximal inspiratory/expiratory pressure – MIP and MEP). Exercise capacity evaluated by Shuttle test (ST) and the quality of life by the Short-form 36 (SF-36) and by the Inflammatory Bowel Disease Questionnaire (IBDQ). **Results:** Patients with CD presented a lower respiratory muscle strength (MIP = -68.93 ± 26.61 vs 29.63 ± 100 cmH₂O, $p = 0.0013$ and MEP = 81.07 ± 30.26 vs 108 ± 25.30 cmH₂O, $p = 0.032$) and a tendency the lower peripheral muscle strength (31.72 ± 8.55 vs 39.00 ± 13.37 kgf, $p = 0.09$). In addition, CD patients presented worse physical capacity on the ST compared to the control group (513.7 ± 237 m vs 983.0 ± 263 m, $p < 0.05$) and worse quality of life in 7 of 8 domains of the SF-36 and in all dimensions of the IBDQ. **Conclusion:** Patients with CD showed muscle functional impairment and poorer quality of life compared to

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healthy control group. These findings suggest that the assessment and maybe interventions in the muscle function must be used in clinical practice.

Keywords: Crohn's Disease. Muscle Strength. Exercise. Quality of Life.

Resumo

Introdução: A doença de Crohn (DC) é uma doença inflamatória intestinal marcada por agudizações e remissões. Manifestações sistêmicas na DC podem estar associadas à síndrome da disfunção muscular esquelética (SDM), a qual é caracterizada por perda de força, queixa de fadiga, limitação ao exercício e prejuízo na qualidade de vida.

Objetivo: Avaliar a força muscular, a capacidade de exercício e a qualidade de vida de pacientes com DC e compará-los com controles saudáveis. **Métodos:** Foram envolvidos 18 pacientes com DC e 12 controles saudáveis pareados por idade e sexo. A força muscular periférica foi avaliada pela força de preensão palmar da mão dominante; e a força muscular respiratória pelas medidas de pressões respiratórias máximas (pressão inspiratória/expiratória máxima – PIM e PEM). A capacidade ao exercício foi avaliada por meio do teste de Shuttle (TS) e a qualidade de vida pelo relacionada à saúde pelo Short Form-36 e pelo The Inflammatory Bowel Disease Questionnaire (IBDQ).

Resultados: A força muscular respiratória mostrou-se reduzida nos pacientes com DC comparado ao grupo controle (PIM = $-68,93 \pm 26,61$ vs $-100 \pm 29,63$ cmH₂O, $p = 0,0013$ e PEM = $81,07 \pm 30,26$ vs $108 \pm 25,30$ cmH₂O, $p = 0,032$) e, com tendência a menor força muscular periférica no grupo de pacientes ($31,72 \pm 8,55$ vs $39,00 \pm 13,37$ kgf, $p = 0,09$). Pacientes com DC apresentaram ainda pior capacidade de exercício no TS ($513,7 \pm 237m$ vs $983,0 \pm 263m$, $p < 0,05$) e pior qualidade de vida comparados aos controles. **Conclusão:** Pacientes com DC mostraram prejuízo funcional muscular e pior qualidade de vida. Estes achados sugerem que a avaliação e possível intervenção da função muscular deve ser adotada na prática clínica.

Palavras-chave: Doença de Crohn. Força Muscular. Exercício. Qualidade de Vida.

Introduction

Crohn's disease (CD) is an inflammatory bowel disease of unknown origin characterized by the focal involvement, transmural and asymmetric of any part of the digestive tract, from mouth to anus (1). It is not clinically or surgically curable and its natural history is marked by acute exacerbations and remissions. The prevalence and incidence in developed countries are around 5:100.000 and 50:100.000 respectively. An estimative of the prevalence in the city of São Paulo found out 14.8 cases per 100,000 inhabitants (2). The CD starts most often in the second and third decades of life, but it can affect any age group.

It is believed that intestinal damage in CD occurs as a result of an exaggerated response of the immune system against its own intestinal flora. It has cyclical course alternating between active and remission phase, with frequent intestinal manifestations of abdominal pain and diarrhea, fistula formation and intestinal obstructive symptoms (3). Besides the manifestations of the digestive system, the CD

can show extra intestinal manifestations, the most frequent being ophthalmic (such as uveitis) of the skin (such as erythema nodosum), rheumatic, and often even osteoporosis and arthralgia, as well as malnutrition, fatigue and state of pre cachexia, which increases the potential for complications (4).

Faced with CD's systemic manifestations, it is suspected that the presence of skeletal muscle dysfunction syndrome (SMD). This syndrome is characterized by atrophy (sarcopenia or pre-cachexia), loss of muscle strength and resistance, which limit the physical capacity. Although its etiology is not yet fully understood, it is likely that the SMD may be multifactorial, involving aspects such as nutritional depletion, systemic inflammation, chronic or repeated use of glucocorticoids, physical deconditioning related to physical inactivity, which may explain the significant symptoms of fatigue in patients with CD (5, 6).

Considering that in patients with CD in the active form the inflammatory peak and the use of glucocorticoids are accentuated, can be hypothesized that peripheral consequences can be even more significant

in this disease's phase, and that coincide with the weight loss and fatigue complaints. Based on these assertions, and given the current limited literature (7 - 10), particularly as regards the assessment of the muscle function, exercise capacity and life quality in patients with CD, it is crucial to study deeper the behavior of these variables in individuals with CD. Thus, this study aimed to evaluate the peripheral muscle strength (grip strength) and central (respiratory muscle strength), the physical capacity and quality of life in patients with CD in the active phase of the disease, as well as compare them to healthy controls.

Methods

Participants

This is a cross-sectional study (conducted from February 2013 to April 2014) whose sample consisted of 18 patients who would start the biological drug therapy with anti-TNF α and therefore classified as the active phase of the disease. These were owned by the Gastroenterology Clinic of the University's Hospital Health Attention Center of the Juiz de Fora Federal University (UH / HAC JFFU) with clinical diagnostics, endoscopic and histological confirmed and 12 healthy control subjects matched by age and sex. The study enrolled patients with active CD, classified as moderate to severe by Harvey-Bradshaw Index (11) > 6, corticoid dependent and / or refractory to immunosuppressants, with complicated fistula and older than 18 and younger than 65 years.

Healthy volunteers were matched by age and sex considering two years more or less in relation to the group with CD, according to the following criteria: be apparently healthy; do not report chronic disease (excluding systemic controlled hypertension) and be able to perform all tests. Were adopted as exclusion criteria for all participants: Pregnant women, with a history of bariatric surgery, extreme diet practitioners (eg.: macrobiotic or vegetarian), with celiac disease, with extensive resection of the small intestine, associated comorbidities, major musculoskeletal limitations which could influence the tests and cognitive losses that could prevent the understanding of the procedures.

Every participant signed a consent form, and all procedures were approved by the Ethics Committee

on Human of the Federal University of Juiz de Fora, under the protocol number 95.125/2012.

Procedures

Peripheral muscle strength - manual dynamometry:

The peripheral muscle strength was obtained from the maximal voluntary contraction manual prehension or simply manual dynamometry (MD) (12). For this measure was used Jamar[®] hydraulic dynamometer.

The guidelines and position used were those recommended by the American Society of Hand Therapists (13). Grip strength of the dominant hand was evaluated and taken three measures with an interval of three minutes between each contraction, with verbal encouragement during the test. The considered contraction force was that in which the patient was able to maintain the maximum reached value for at least three seconds.

Respiratory muscle strength:

The respiratory muscle strength evaluation was taken by the manovacuometer with range of \pm 300 cmH₂O (Gerar[®], São Paulo - Brazil). The measures of maximal respiratory pressures MIP and MEP were performed in accordance with previous determinations (14), while the volunteers were seated, using a nose clip and mouthpiece between his lips. The measurement was considered completed when the individual performed five acceptable measures, and among these, a minimum of two reproducible ones. The last value found can not be higher than the other, when it occurred, the maneuver was repeated until the last value was shorter than or equal to the last, considering the learning effect. The acceptable maneuvers were those with no air leaks between the lips, with a maximum pressure support of at least one second, and reproducible, in other words, with a variation shorter than or equal to 10% of the highest value. All strength ratings of the respiratory muscles were made by the same person, properly trained to do so. The values obtained were compared with the reference values determined by Neder et al. (15).

Physical capacity:

The maximum physical capacity was assessed by the incremental Shuttle test (ST) (16). The ST consists of walking on flat ground, running repetitively a distance of 10 meters around a marking of two cones. The only acoustic sound indicates the time in which the individual must go through the predetermined distance, reaching the cone and change direction, returning to the other cone, while the triple acoustic signal indicates the need to increase the speed to cover the distance between the cones.

At every minute, the time between the acoustic signals reduces so that the individual should increase the walking speed to reach the cone at the right time (increased every minute of 0,17m/s). The end of test is determined when the individual fails, for the second (17) to complete the distance between the cones within the allowed time, that is, when is more than 0.5m cone when the beep sound or when shows symptoms of fatigue of the lower limbs or intolerable dyspnea (16). It is therefore an incremental test with stages up to 12 levels of speed that produces a similar physiological load test similar to an incremental cycle ergometer test (18).

The values obtained were compared with the reference values determined by Probst et al. (17), given by the following formula: Predicted distance = $1449.701 - (11.735 \times \text{age}) + (241.897 \times \text{gender}) - (5,686 \times \text{BMI})$, where: male = 1, female = 0. The outcome measures of this test were the total distance covered, the stage level achieved in the test and the percentage of the predicted distance.

Quality of life:

The health-related quality of life in general terms was evaluated in both groups of patients and controls through the health-related quality of life - Short Form 36 (SF36). The SF-36 is a generic questionnaire, validated in Portuguese (19) and distributed in eight domains: limitations in physical activity due to health problems; limitations for physical health problems; Vitality on energy and fatigue; pain in the body; general mental health; limitations due to emotional problems; perception of general health; and social aspect. The score for each of the domains of the SF-36 questionnaire ranges from zero (worst health status) to one hundred (better health status).

Additionally, in the group of patients with CD was used the Inflammatory Bowel Disease Questionnaire (IBDQ), originally created by Gyatt et al (20). This questionnaire is specific for intestinal inflammatory diseases (IID) such as CD and ulcerative colitis, has been translated, validated, and tested the psychometric properties for Portuguese (21). It consists of 32 questions that evaluate different aspects of life quality for the previous 15 days, and are grouped into four areas: intestinal symptoms and systemic, social function and emotional. Originally, the score is obtained according to a Likert scale of 1 to 7, with 1 corresponding to the worst health status and 7 to the best health. The sum of points obtained in each domain takes place, and the total sum of each domain will result in the patient's overall score. The total score can range from 32 to 224. Based on clinical studies using IBDQ (22 - 24), we follow the rating for the quality of life in this study: ≥ 200 = excellent; 151-199 = good; 101-150 = regular; ≤ 100 = bad.

Data analysis:

The data were tabulated and analyzed using SPSS 17.0 for Windows (SPSS Inc, Chicago, USA). Data were expressed average \pm standard deviation or median (and minimum-maximum) when appropriate. Normality was tested by the Shapiro-Wilk test. For comparison between groups was performed Student t test unpaired or Mann-Whitney, as the data were parametric or not, respectively. The probability for type I error was assumed to be 5% in all tests ($p \leq 0.05$).

Results

Initially, 29 patients with CD were recruited, 11 were excluded according to the criteria: morbid obesity (1), comorbidities (4), depression (1), extensive resection of the bowel (1), refusal to participate in the study (4). However, the final sample consisted of 18 patients with CD and 12 healthy controls.

All patients with CD were in the active stage of the disease characterized by Harvey-Bradshaw index of 6.7 and by the repetitive or chronic use of glucocorticoids in the last 6 months, besides the use of azathioprine since the disease's diagnosis.

Table 1 shows the demographic characteristics of muscle strength and physical capability of the sample. It was allowed to pair a control with the same age and sex for each two patients, which explains the difference in the sample size of each group. It is observed that there was no difference between the average age of both groups. In relation to BMI was difference, wherein the average BMI of the group with CD lower than the average healthy controls.

In Table 1 are also shown the muscle strength and physical function data in both groups. Although it can be observed a tendency of handgrip to be lower in patients with CD, this was not significantly different ($p = 0.09$). Furthermore, shown differences between the values of both MIP as MEP between the patient and control groups, showing lower values for the CD group. As for the analysis of physical capacity by TS - distance, predicted percentage and reached

level - showed differences between groups, and the CD group traveled less distance if compared to the control group.

The Table 2 have shown the scores obtained in the 8 domains of the life quality questionnaire related to the health SF-36. Of the 8 domains, only the domain "Limitations due to emotional problems" showed no difference. In the other, the CD group had worse life quality self-report compared to the control group.

In relation to the domains of the life quality specific questionnaire for inflammatory bowel disease, the IBDQ, this was applied only in patients with CD. The scores in medians and minimum and maximum values of the domains were systemic aspects 44 (28 - 70); intestinal aspects 19 (8 - 34); social aspects 27 (7 - 35); emotional aspects 14 (0 - 21); and complete 94 (58-154). All patients had values corresponding to the low quality of life (total score <170).

Table 1 - Demographic characteristics of muscle strength and physical capability of the sample

	CD Group	Control Group	Value of <i>p</i>
Demographic data			
Age (in years)	38.56 ± 13.69	37.30 ± 13.22	0.834
BMI (Kg/m ²)	22.45 ± 2.97	25.52 ± 3.19	0.018*
Gender	11f/7m	7f/5m	--
HBI	6.7	--	--
Respiratory Muscle Strength			
MIP (cmH ₂ O)	-68.93 ± 26.61	-100 ± 29.63	0.013*
Maximum Predicted IP%	64.26 ± 21.70	94.10 ± 28.16	0.011*
MEP (cmH ₂ O)	81.07 ± 30.26	108 ± 25.30	0.032*
Maximum Predicted EP%	72.28 ± 27	97.56 ± 24.98	0.046*
Peripheral Muscle Strength			
Handgrip Strength (Kgf)	31.72 ± 8.55	39.00 ± 13.37	0.09
Physical Capacity			
Covered Distance (m)	513.7 ± 237	983.0 ± 263	0.001*
Predicted Distance (%)	55.09 ± 22.90	102.24 ± 19.62	0.001*
Shuttle Level	8.11 ± 2.16	11.8 ± 1.93	0.001*

Table 2 - Characterization of health-related quality of life by SF-36

SF-36 Domains	CD Group	Control Group	Value of <i>p</i>
Functioning Capacity	70 (0-100)	100 (75-100)	0.001*
Physical Aspects Limitations	50 (0-100)	100 (50-100)	0.004*
Pain	51 (10-100)	92 (51-100)	0.006*
General Health Status	52 (42-82)	88.5 (62-100)	0.000*
Vitality	55 (10-100)	67.5 (55-95)	0.017*
Social Aspects	50 (12.5-100)	93.75 (25-100)	0.049*
Emotion Aspects Limitations	66 (0-100)	100 (0-100)	0.10
Mental Health	60 (20-96)	84 (48-92)	0.023*

Discussion

The results of this study show that patients with CD in the active phase of the disease show: reduced muscle strength, reduced physical capacity and loss on life quality when compared to healthy controls. This study aimed to evaluate muscle function, physical capacity and life quality in patients with CD in the active phase of the disease, once that at this stage the inflammatory peak and malabsorption of nutrients lead to anemia, malnutrition, fatigue and longer home confinement time due to increased bowel frequency (4).

Although the drug treatment done with corticosteroids assists the inflammation control in the active phase of the disease, it is known that chronic or repeated use of this leads to the lysis of myofibrils which may compromise the physical function and life quality of these patients (25 - 26). This study showed a reduction in respiratory muscle strength and a tendency to decrease in peripheral muscle strength in patients with CD, which can be explained by the range of factors that involves the inflammatory, nutritional and therapeutic aspects of the disease.

Muscle strength and exercise capacity are indicative parameters of muscle function. The muscle weakness and fatigability results in loss of performance and consequently worst quality of life. Muscle strength is derived from the motor units composed of fibers of slow and fast twitch, i.e. type I fibers, IIa and IIb, respectively. This property, strength, depends on some intrinsic characteristics, such as: (i) the number of fibers innervated by a motor neuron; (ii) cross-sectional area of muscle fibers within the unit; (iii) percentage of specific fibers of muscle strength; (iv) number of motor units recruited; (v) contraction velocity and (vi) muscle tensio-length relation. Changing any of these properties results in muscular weakness, which reduces exercise capacity and increases the intensity of the symptoms of fatigue (27).

Several studies determine cofactors that lead to loss of muscle strength in chronic inflammatory diseases (27 - 29). The pathological mechanisms that involves systemic inflammation, inadequate nutrition, hormonal dysfunction or adverse effects of corticosteroid drugs can lead to atrophy, chronic inactivity and fatigue, further corroborating the disuse atrophy, which are the probable etiology of muscle dysfunction in patients with CD (26 - 29).

Other studies in patients with other chronic, also, inflammatory diseases showed associations

peripheral, respiratory and muscle strength reductions with the severity of the disease, with postoperative complications, worsening of life quality, sarcopenia and with an inflammatory markers increase (30, 31). Spruit et al. (29) observed a negative relationship between the peripheral muscle strength reduction and the elevated systemic inflammation in acute exacerbation of COPD. This analogy can be made between patients with exacerbated COPD and CD patients in the active stage of the disease, when the inflammatory stress is enhanced, the use of hormonal anti-inflammatory therapy and greater physical inactivity occurs.

Although the inflammatory profile of patients in this study was not objectively assessed, we assume that according to the HBI, which indicates the stage of the disease in which the patient is (active or remission), all patients involved in this study were in the active phase of the disease determined by HBI 6.7. At this stage of the disease, the inflammatory stress and the exacerbation of intestinal and extra intestinal symptoms are more pronounced requiring corticosteroid therapy (4).

It is well known that in chronic inflammatory diseases the continued use of corticosteroids causes the involvement of the proximal muscles occurs prior to the distal (26, 32). In this logic, one could suggest that the manual dynamometry can neglect peripheral muscle weakness by assessing a limited muscle group (upper limbs), especially if the disorder involves primarily proximal muscles or yet locomotor muscles. In this context, it can be assumed that this method has low sensitivity in the evaluation of muscle functional deficit, suggesting that specific segmental reviews of proximal muscles and lower limbs should be considered.

On the other hand, the respiratory muscle strength showed differences between the groups, and both the average values of MIP as MEP were lower in the CD group, which seems to be more consonant with the proximal muscles. The reduction in expiratory muscle strength (MEP) brings indicative that patients have worse performed of abdominal muscles, muscles that is enabled in the forced expiration, in cough and defecation (33). The reduction in inspiratory muscle strength suggests that the diaphragm and the accessory inspiration muscles (sternocleidomastoid, scalene, intercostal) also showed worse performance when compared to the control group. However, the reduction in respiratory muscle strength observed in

patients with CD does not have to date clinical importance, because although with lower values than controls, they do not suggest muscle fatigue, mechanical ventilatory insufficiency, or perception of dyspnea that justify specific intervention of this muscle group. After literature review, only one case report of patient with CD and peripheral and respiratory muscle weakness was found, although in this case the patient had polymyositis associated (34). However, our findings may help to elucidate how the muscles can be affected heterogeneously in this population.

Although the muscle function of the locomotor muscles have not been used, it is known that the lower limbs muscle strength reduction is an event that leads to intolerance to exercise, which is intensified in the active disease phase with physical deconditioning. In the comparison between groups, the CD group traveled less distance in the ST than the control group, which corresponded to about 50% of the predicted distance. Otto et al analyzed the physical capacity of 534 adults with various gastrointestinal diseases, including IBD, by maximum cardiopulmonary effort test in the preoperative evaluation and concluded that patients with CD had lower anaerobic threshold if compared to cancer patients and other diseases colorectal (7). These findings corroborate the results of the reduced physical capacity in patients with CD found in this study. There is evidence that patients with CD have a lower proportion of muscle fibers type I, fibers that determine exercise tolerance (35). The physical capacity reduction can be attributed to high levels of pro-inflammatory cytokines, by the high frequency of daily bowel movements, by the nutritional malabsorption, by inactivity and by the use of systemic corticosteroids (7).

Similarly, Ploeger et al. (8) found that pediatric patients with inflammatory bowel disease using corticosteroids had aerobic capacity reduced when compared to those not taking the drug, despite the lean body mass is not decreased, showing the influence of drug therapy in the exercise capacity of these patients.

In the present study it was even observed that in patients with CD, the life quality related to health was worse in 7 of the 8 areas that compose it. The decrease in quality of life in these patients is easily understood by the frequent manifestation of intestinal symptoms such as diarrhea and abdominal and extra bowel pain, as weight loss, anemia, fever, arthralgia,

muscle dysfunction, with a consequent loss in physical activity and social activities (8). Complementing the generic life quality questionnaire (SF-36), the specific questionnaire quality of life for IBD, the IBDQ, has also been applied in patients with CD, and this pointed to a poor life quality of those with a score of 94 (<100 points).

Different studies show that life quality is compromised in patients with IBD (8, 35, 36). Bernklev et al. (37) compared the life quality auto account of 514 IBD patients (348 with ulcerative colitis and 166 with CD) and 2323 healthy Norwegians. The results showed that in patients with UC the scores of 6 of the 8 domains of the SF-36 were below the healthy population and in patients with CD were below in 7 of the 8 domains.

Despite the absence of direct measurements, such as tissue biopsy, to confirm enzymatic, biochemical and metabolic alterations of muscle fibers, the results presented here, supported in the literature subsidies, allow us to guess that CD patients have muscle dysfunction with repercussions in physical capacity and life quality of thereof. This finding carries important clinical implications, because from the assumption physical rehabilitation strategies should be considered in order to improve physical function and life quality of this population.

The present study has limitations such as the small sample size, the involvement of only patients in the active phase of the disease and its design of the cross-sectional study. Although the sample was modest, it is a disease of low prevalence in the population, but nonetheless was possible to detect significant differences in most variables. In this hand, it is crucial to continue this line of research and perform another study phase with longitudinal templates, to investigate the impact of therapeutic interventions in CD patients with muscular dysfunction.

Conclusion

From the observed results we can conclude that CD patients have impaired muscle strength, in the exercise capacity and life quality compared to healthy subjects. While it is necessary more studies investigating the muscle function in patients with CD, the data from this study suggest that the assessment of muscle function should be adopted in clinical practice.

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Received in 07/24/2015

Recebido em 24/07/2015

Approved in 08/11/2016

Aprovado em 11/08/2016