NARRATIVE REVIEW

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Inflammatory bowel disease and sarcopenia: a focus on muscle strength – narrative review

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HIGLIGHTS

- Muscle strength decline is a crucial factor for the course of sarcopenia in inflammatory bowel disease (IBD) patients.
- There is a need to discuss the association between IBD and sarcopenia focusing not only on changes of muscle mass, but also on muscle strength.
- A narrative review was conducted in order to present the set of factors with impact in both muscle strength and IBD.
- Inflammation, reduced nutrient intake and malabsorption, changes in body composition and gut microbiota dysbiosis are most likely the main factors with impact on muscle strength in IBD patients.

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ABSTRACT – Inflammation, changes in nutrient absorption and gut dysbiosis are common conditions in patients with inflammatory bowel disease. These factors may lead to variations in macro- and micronutrients and, particularly, to an imbalance of protein metabolism, loss of muscle mass and development of sarcopenia. This narrative review aims to present the set of factors with impact in muscle strength and physical performance that may potentially mediate the relation between inflammatory bowel disease and sarcopenia. Studies that associated changes in muscle strength, sarcopenia and inflammatory bowel disease were selected through a literature search in databases Medline, Pubmed and Scielo using relevant keywords: muscle strength, physical performance, sarcopenia and inflammatory bowel disease. Chronic inflammation is currently reported as a determinant factor in the development of muscle atrophy in inflammatory bowel disease. In addition, strength decline in inflammatory bowel disease patients may be also influenced by changes in body composition and by gut dysbiosis. Measures of muscle strength and physical performance should be considered in the initial identification of sarcopenia, particularly in patients with inflammatory bowel disease, for a timely intervention can be provided. Presence of proinflammatory cytokines, high adiposity, malabsorption and consequent deficits of macro and micronutrients, loss of muscle mass, and gut dysbiosis may be the main factors with impact in muscle strength, that probably mediate the relation between inflammatory bowel disease and sarcopenia.

Keywords – Inflammatory bowel disease; muscle quality; muscle strength; physical performance; sarcopenia.

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated disorder characterized by chronic inflammation of the gastrointestinal tract, classified into two primary subtypes: Crohn's disease (CD) and Ulcerative colitis (UC)[1-5]. Genetic and environmental factors cause imbalances in both immune system and gut microbiota, acting synergistically for the development of IBD[1-5]. In turn, sarcopenia is a disease characterized by loss of muscle strength, muscle mass, and function, and thus low physical performance[6]. Sarcopenia has been associated with several negative outcomes such as longer length of hospital stay[7] and higher hospitalization costs[7].

The risk of developing sarcopenia is high in IBD patients due to inflammation, changes in nutrient intake and absorption, and changes in body composition[1-5]. According to a recent systematic review, the incidence of sarcopenia can reach approximately 60% in patients with IBD[8]. Individuals with both IBD and sarcopenia have a worse quality of life and an increased risk of surgical complications[7-10]. The relation between IBD and sarcopenia was discussed in two previous reviews, however, these reports mainly focused on changes in muscle mass[1,4]. Muscle strength, particularly handgrip strength, is often reduced in both CD and UC patients compared to healthy individuals[11,12]. In addition, low muscle strength is currently the first criterion to identify probable sarcopenia since the reformulation of its diagnostic criteria in 2018 by the European Working Group on Sarcopenia in Older People (EWGSOP2)[6]. Therefore, there is a need to discuss the impact of changes in muscle strength and physical performance in IBD patients[4].

This narrative review aims to present the set of factors with impact in muscle strength and functionality that may potentially mediate the association between IBD and sarcopenia.

Sarcopenia assessment

According to the EWGSOP2, muscle strength can be assessed by handgrip strength, using a dynamometer; muscle quantity or mass can be estimated using techniques such as bioelectric impedance analysis or dual-energy x-ray absorptiometry; muscle function can be assessed through physical performance using functional tests such as the Short-Physical Performance Battery or gait speed[6]. Sarcopenia is present when the patient presents low muscle strength, low muscle mass and/or low physical performance[6].

Muscle quality is an ongoing concept that mainly focuses on muscle strength and functionality than on muscle mass, in addition to the presence of intramuscular fat and other characteristics of muscle tissue[6]. Loss of muscle strength can be detected earlier than loss of muscle mass[13], and the risk of mortality presents a stronger association with loss of muscle strength than with loss of muscle mass[14].

Factors with impact in both inflammatory bowel disease and muscle strength

Inflammation plays a complex key role in IBD and in muscle strength decline. Additionally, reduced nutrient intake and malabsorption, malnutrition (undernutrition and obesity), and gut microbiota dysbiosis increase the predisposition to sarcopenia in IBD patients (TABLE 1).

TABLE 1. Summary of factors that affect muscle strength and functionality in patients with inflammatory bowel disease.

Factor	Observed effect	References
Inflammation	Increase of pro-inflammatory cytokines, particularly TNF-α, (IL)-6 and (IL)-12	(15,18-20)
Reduced nutrient intake and malabsorption	Macronutrients deficiency, particularly protein	(2,48)
	Minerals deficiency, particularly iron and magnesium	(25,28,31,48)
	Vitamins deficiency, particularly vitamin $B_{12,}$ folic acid and vitamin D	(24,35-43,48-50,85,86)
Changes in body composition	Decrease in muscle mass; Increase in adiposity, particularly intermuscular fat	(56,59-63)
Gut microbiota dysbiosis	Increase in the abundance of inflammatory bacterial species, particularly within the phyla Proteobacteria	(71-75)

TNF: tumor necrosis factor-alpha; IL: interleukin.

Inflammation

Pathogenesis of IBD implies higher levels of pro-inflammatory cytokines that change protein turnover with degradation of myofibrillar proteins[15]. The proinflammatory cytokines emit signals that block the anabolic mammalian target of rapamycin complex 1 (mTORC1) pathway, reducing protein synthesis[16]. In addition, an inflammatory environment promotes the formation of reactive oxygen species, leading to contractile muscle dysfunction, muscle atrophy and loss of muscle strength[17].

The tumor necrosis factor-alpha (TNF-α) is an inflammatory cytokine inducing necrosis or apoptosis that has an important role in the pathogenesis of IBD, also providing a significant endocrine stimulus for contractile dysfunction in chronic inflammation[15,18].

Interleukin (IL)-6 is another proinflammatory cytokine associated with muscular damage. It is known that muscle atrophy may be a consequence of a low-grade chronic inflammation status and of an imbalance of energy homeostasis favored by IL-6[15,18].

In turn, and IL-12 has also been is a target for the medical treatment of CD and has also been associated with contractile dysfunction. IL-12 encourages T cell proliferation and cytotoxic activity leading to skeletal muscle degeneration[19-22]. Chen et al. demonstrated that muscle strength and gait speed were negatively associated with IL12[20].

The decline of muscle strength may be a consequence of chronic lowgrade systemic inflammation, but a systemic inflammatory condition may also occur as direct result of low muscle mass and strength[15-17]. Proinflammatory cytokines impair muscle strength and physical performance in IBD patients by increasing protein catabolism, reducing muscle synthesis, inducing muscle atrophy, and decreasing contractile response, as well as stimulating an immune-mediated response that impairs muscle regeneration.

Higher pro-inflammatory cytokine levels in IBD patients may lead to sarcopenia once an association between inflammatory parameters and sarcopenia has already been established in other contexts[6]. However, there are few studies that investigated the relation between inflammation and particular changes in muscle strength or physical function. Maybe because most of the studies report a diagnosis of sarcopenia mainly based on the quantity of muscle mass instead of muscle strength. Most of the published evidence on sarcopenia in IBD patients focuses mainly on muscle mass quantity as diagnosis criterion of sarcopenia, therefore more studies emphasizing muscle function over muscle mass quantity are needed.

Reduced nutrient intake and malabsorption

The inflammatory condition in IBD patients causes intestinal malabsorption with consequent macro- and micronutrient deficiencies that lead to muscle strength decline[2,3].

Low plasma levels of iron, magnesium, as well as B vitamins, folic acid, and vitamin D are the most common deficiencies in IBD patients[23,24]. Iron deficiency is a recognized cause for anemia, which is the most frequent extraintestinal manifestation of IBD[25]. In addition, iron deficiency and anemia cause loss of the muscle oxidative capacity that has direct implications in muscle strength decline[26]. An inverse association between anemia and handgrip strength was reported in a large sample of Korean adults, particularly strong for males and those aged ≥65 years[27]. Handgrip strength, used for the diagnosis of muscle weakness, has been proposed as a useful technique for the screening of patients with anemia[28].

The World Health Organization cut-offs for anemia also apply to IBD patients: hemoglobin levels <13 g/dL (hematocrit <39%) in males, <12 g/dL (hematocrit <36%) in nonpregnant females, and <11 g/dL (hematocrit <33%) in pregnant females[29]. Regarding blood iron concentration, for patients with quiescent IBD without evidence of inflammation, iron deficiency is defined as serum ferritin <30 g/L or transferrin saturation <16%. For patients with active disease, the cut-off for serum ferritin is defined as <100 g/L[30].

Low levels of magnesium have been reported in IBD patients[31]. Regarding magnesium impact in muscle strength and performance, patients with severe hypomagnesemia frequently notice muscle cramps[31]. Magnesium mediates muscular contractions by opposing calciumbinding proteins, even though role in the pathophysiology of muscle cramps is not well known[31]. Some authors suggested that serum magnesium concentration should be at least 0.75 mmol/L to avoid hypomagnesemia condition[32].

In addition, lower intakes of magnesium have been independently associated with lower appendicular muscle strength[33,34].

The deficiency of B vitamins is also prevalent in IBD patients with effects on the peripheral nervous system, and with loss of motor function and strength decline[35]. Vitamin B_{12} deficiency was defined as a vitamin B_{12} serum level below 180 ng/L, and the cut-off for folate deficiency was defined as a serum level below 4 ng/mL (9.064 nmol/L)[36]. Lower intakes of vitamin B_{12} and folate were associated with higher risk for developing sarcopenia[24] and in subjects with higher serum vitamin B_{12} and folate concentrations, higher leg muscle strength was also observed[37].

Regarding vitamin D, approximately 70% of CD patients and up to 40% of patients with UC are affected by its deficiency[38]. Vitamin D deficiency seems to be associated with activity and pathogenesis of IBD[38,39]. According to the US Institute of Medicine, adequate serum levels of vitamin D (25hydroxyvitamin D) should be to at least 50.0 nmol/L[40]. Values between 30.0 and 49.9 nmol/L indicate risk of inadequacy, and values less than 30.0 nmol/L indicate risk of deficiency[40]. Vitamin D deficiency alters the immune response and compromises the integrity of the mucosal barrier, favoring the progression of both IBD and sarcopenia[39]. Vitamin D is involved in the growing and differentiation of muscle cells since it contributes to lower production of myostatin[41-43]. Therefore, the loss of muscle strength is a consequence of vitamin D deficiency that leads to atrophy and fibrosis of type IIA muscle cells[41]. The expression of vitamin D receptor (VDR) seems to be impaired in the skeletal muscle cells of IBD patients affecting muscle homeostasis[41]. Higher expression of VDR decreases the factor nuclear kappa B (NF-kB), tolllike receptor (TLR) 2 and TLR4, and TNF-α levels, promoting the activation of muscle contraction and mitochondrial function[41].

The association between lower plasma levels of vitamin D and lower muscle strength is still not consensual among epidemiological studies. In community-dwelling Portuguese older adults, the risk of vitamin D deficiency was directly associated with the lowest values of handgrip strength and gait speed[44]. An analysis of pooled data from randomized controlled trials showed that vitamin D supplementation had a small but significant positive effect on muscle strength[45] and on physical performance assessed by Timed Up-and-Go test[46]. These effects are more evident among participants with low levels of vitamin D at baseline[45,47]. However, the design of upcoming studies should explore the association between low vitamin D levels and low muscle strength, in IBD patients.

IBD patients with active disease that reduce oral ingestion due to anorexia or gastrointestinal symptoms also present increased risk of macronutrient (protein, fat and/or carbohydrates) deficiencies, with a consequent negative impact in strength and body composition[2]. In IBD patients is common a lower intake and bioavailability of essential amino acids for muscle proliferation, with a deficient anabolism, inducing muscle atrophy[41]. A chronic poor dietary intake increases the protein turnover rate and intestinal loss of macronutrients during phases of active disease or as result of disease treatments[48]. Specifically, leucine deficiency causes a reduced synthesis of muscle protein[49] since this amino acid is an important factor to activate mTOR pathway[50]. The assessment of nutritional status biomarkers in clinical practice may be useful for an early identification of muscle strength decline and poor muscle quality in IBD patients.

Changes in body composition

Malnutrition and sarcopenia are common in patients with IBD[51,52]. Undernourished IBD patients present less than 60% of muscle strength as compared to healthy individuals[53] leading to an increase of clinical complications and infections[54], higher length of hospital stays, higher number of readmissions, and increased risk of mortality[55]. According to Adams et al. and Zhang et al., IBD patients with sarcopenia have lower body mass index and skeletal muscle index than patients with a normal body mass composition[56,57]. However, overweight and obesity prevalence has increased in IBD patients[58]. This information is confirmed by results from some studies: a study conducted by Flores et al. in 581 IBD patients showed that approximately 32.7% of patients were obese, of which 30.3% were CD patients and 35.2% were UC patients[59]. In addition, up to 20% of sarcopenic patients are also overweight or obese[56]. A high prevalence of sarcopenic obesity was particular-

ly detected among CD patients[42]. Therefore, in IBD patients, sarcopenia must be assessed independently of the patient's body mass index.

Proinflammatory cytokines produced by adipocytes and free fatty acids are related to the pathogenesis of IBD and sarcopenia[15,60]. Intramuscular lipids and their derivatives induce mitochondrial dysfunction characterized by impaired βoxidation capacity and increased reactive oxygen species formation providing lipotoxic environment and insulin resistance capable of inducing muscle dysfunction by auto and paracrine manner[61]. Interestingly, an increase in intermuscular fat was associated with a higher loss of muscle strength than muscle mass, regardless of changes in weight or subcutaneous fat[62]. Recently, fat mass was reported as independently and inversely related to jump test performance in middle-aged and older adults[63]. Therefore, adiposity has clinical implications for muscle performance and should be explored also in the context of IBD patients.

Gut microbiota dysbiosis

The gut microbiota establishes a symbiotic relation with the host, mutually beneficial in a healthy environment[64]. The homeostatic equilibrium of the gut microbiota may be affected by both host and environmental factors leading to dysbiosis, i.e., an altered microbiota composition. Dysbiosis may contribute to IBD pathogenesis as consequence of a breakdown in the equilibrium between putative protective and aggressive microbial species[65]. Protective species interact with the immune system contributing to the homeostatic mechanism while aggressive species promote non-immunogenic inflammatory reactions, disturbing homeostasis. An abnormal immune response to the gut microbiota in genetically susceptible individuals is one of the most accepted theories behind the etiology of IBD[66]. Dysbiosis is commonly linked to inflammatory cell activation and impaired epithelial barrier function which is a hallmark in IBD. Most of the studies in IBD patients reported alterations in the abundance of specific bacterial taxa within the phyla Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria, that includes a variety of enteric pathogenic species, with a reduction of protective groups combined with an expansion of putative inflammatory groups[67-70]. The dysbiotic profile of gut microbiota under chronic intestinal inflammation has been previously reviewed[70].

The increased abundance of inflammatory bacterial species in IBD, such as *Escherichia coli* (Enterobacteriaceae, Proteobacteria), contribute to the disruption of the intestinal barrier integrity and increased intestinal permeability. Several enteric pathogens can alter the intestinal epithelial tight junctions[71], essential for the regulation of the paracellular movement of substances (e.g., water, ions, solutes, and small molecules) across the intestinal epithelium[72]. Increased intestinal permeability facilitates the passage into the circulation of microbial products and endotoxins, such as lipopolysaccharide (LPS). LPS, a component of the outer membrane of gram-negative bacteria, promotes inflammatory signaling and skeletal muscle changes, characteristic of the aging muscle phenotype[73]. In fact, the higher abundance of gram-negative Proteobacteria, in the gut microbiota of middle-aged males demonstrated a significant negative association with the handgrip strength, while a positive association was observed between the gram-positive Actinobacteria and skeletal muscle strength[74]. Furthermore, higher intestinal permeability and presence of LPS are associated with a decline in skeletal muscle strength[74]. LPS binding protein has been previously associated with impaired physical function and inflammation in healthy older adults[75]. These studies suggest that intestinal permeability as a determinant predictor of muscle recession and sarcopenia.

The gut microbiota of older and frail individuals is characterized by lower butyrate production, loss of membrane integrity, higher interindividual variability and presence of pathogenic gramnegative bacteria, providing the individual with higher susceptibility to the development of sarcopenia. Studies on the gut--muscle axis in sarcopenia are limited in humans. Recent data suggest a role of the gut microbiota on the maintenance of muscle strength[76] and physical functioning[77,78]. Older adults with different functional states demonstrated higher abundance of the genus *Prevotella* and *Barnesiella* in individuals with higher muscle strength, when compared with older adults that had reduced muscle strength[76]. Moreover, the transfer of fecal samples from these older adults into germ-free mice resulted in a significantly increased

grip strength in high-functioning colonized mice, when compared with mice with lowfunctioning[76]. *Prevotella* are increased in young professional athletes[79], and both *Prevotella* and *Barnesiella* are higher in less frail, when compared with more frail older adults[80,81], supporting the hypothesis that these bacteria may be involved in mechanisms related to the maintenance of physical function.

The administration of the probiotic strain *Lactobacillus plantarum* TWK10 improved muscle strength, exercise endurance, and overall body composition in both animal models and healthy humans[82,83]. In addition, the administration of *L. plantarum* attenuated aging-related muscle weakness by improving muscle quality and increasing muscle glycogen levels in naturally aging mice[84].

Gut microbiota-targeted therapies such as the use of probiotics and prebiotics are potential novel strategies to enhance muscle mass, muscle strength and physical performance, and simultaneously contribute to the treatment of IBD. The recently published global guidelines from the World Gastroenterology Organization suggest that the use of probiotics may be safe and as effective as conventional therapy in the treatment and maintenance of mild to moderately active UC in both adult and pediatric patients[85,86]. On the contrary, there is no current evidence to suggest that probiotics are beneficial for induction or maintenance of remission in CD[85], due to a lack of well-designed randomized controlled trials in this field of study[87]. However, long-term studies involving administration of synbiotics have demonstrated promising results in active CD and UC[88,89,90].

The imbalance of microbial homeostasis leads to the colonization and invasion of opportunistic pathogens in the gut, which increases the risk of the host immune response and promotes the development of IBD[70]. In addition, gut dysbiosis is related to detrimental of muscle growth, but its contribution to changes on strength and physical performance was still little explored. It is critical to identify the specific pathogens related to the pathogenesis of IBD and understand whether these pathogens have impact on the development of sarcopenia.

Nutritional-related interventions

Routine micronutrient supplementation is not crosswise for IBD patients. Nutritional intervention in IBD should be individualized and focus mainly on replacing micronutrients when a deficiency is diagnosed even in the absence of sarcopenia. For example, iron supplementation is recommended in IBD patients when iron-deficiency anemia is present[48]. Even in anemia condition, the estimation of iron need varies because it is usually based on baseline hemoglobin and body weight of IBD patients[48].

Concerning other micronutrients, it is already possible to mention more concrete replacement values, but that depends more on the stage of the disease and the treatment options, surgical and/or pharmacological, than on the presence of sarcopenia. For example, IBD patients with clinical deficiency of Vitamin B_{12}, particularly when submitted to resection of parts of ileum, should receive 1000 mg of this vitamin by intramuscular injection every other day for a week and then every month for life[48,91]. In addition, the European guidelines also advise oral administration of folate in IBD patients on methotrexate, 5 mg once weekly 24-72 h after the methotrexate treatment, or 1 mg daily for 5 days per week[48,92].

Regarding macronutrient deficiencies, protein requirements are increased in both active IBD patients and sarcopenic patients, and intake should be increased to 1.2–1.5 g/kg/d compared to recommendations for general adult population[48,93]. After an inflammatory episode, dietary protein needs in IBD patients may be increased for gastrointestinal mucosal healing, being used as building blocks for macromolecule synthesis in the wounded mucosal area, and for total muscle protein synthesis thus preventing strength decline and sarcopenia[94]. Paradoxically, an excessive amount of dietary protein may result in an increased intestinal production of potentially deleterious bacterial metabolites that negatively affect IBD[94]. In older patients with sarcopenia, the administration of a leucine-enriched amino acid supplement, during eight weeks, significantly improved the performance of activities of daily living and increased muscle strength[95]. In the future, clinical trials should be conducted to evaluate the effect of leucine supplements in the prevention and treatment of sarcopenia in IBD patients.

In IBD patients, fat malabsorption is also obser-

ved because of decreased reabsorption of bile acids that are deconjugated by bacteria in the colon[48]. However, according to the recent European guidelines, dietary supplementation, e.g., n-3 fatty acids, shall not be advised to support the maintenance of remission in patients with IBD[48], but may be of interest in the case of sarcopenic patients without IBD[93]. Regarding carbohydrates, some authors consider that supplementation with selected fermenting carbohydrates, promoting specific bacteria and/or metabolites, may be beneficial for IBD patients[48]. Carbohydrates from the oligosaccharides and inulin classes have been the most studied[48].

CONCLUSION

Relevant mechanisms associated with the pathophysiology and presentation of IBD are simultaneously related to the loss of muscle strength and function leading to a poor muscle quality and consequent sarcopenia. However, there is a lack of studies that investigate simultaneously both conditions, IBD and low muscle strength, and this was the main limitation of this review. In future it will be necessary to use the same study design to clarify which factors impact muscle quality in IBD patients, particularly muscle strength and physical performance.

An increase of clinical complications due to the simultaneous presence of sarcopenia was observed in IBD patients, particularly in elderly patients. There is a need to incorporate muscle strength and physical function measures into the early identification of sarcopenia in IBD patients. The strength decline is a crucial factor for the course of sarcopenia, which in turn, is a frequent comorbidity in IBD patients.

The presence of proinflammatory cytokines, the reduced nutrient intake and malabsorption, undernutrition, obesity, and gut microbiota dysbiosis may represent the main factors with impact in muscle strength, that probably mediate the relation between IBD and sarcopenia.

Authors' contribution

Conceptualization and methodology: Mendes J and Sousa AS. Writing original draft preparation: Mendes J. Writing review and editing: Mendes J, Simões CD, Martins JO; Sousa AS. Supervision: Mendes J and Sousa AS.

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Mendes J, Simões CD, Martins JO, Sousa AS. Doença inflamatória intestinal e sarcopenia: um foco na força muscular – revisão narrativa. Arq Gastroenterol. 2023;60(3):373-82.

RESUMO – Inflamação, alterações na absorção de nutrientes e a disbiose intestinal são condições comuns em indivíduos com doença inflamatória intestinal. Estes fatores podem levar a variações corporais do teor de macro e micronutrientes e, em particular, a um desequilíbrio no metabolismo de proteínas com perda de massa muscular e desenvolvimento de sarcopenia. Esta revisão narrativa visa apresentar o conjunto de fatores com impacto na força e função muscular que podem potencialmente mediar a relação entre doença inflamatória intestinal e sarcopenia. Estudos que associaram as alterações de força muscular, sarcopenia e doença inflamatória intestinal foram selecionados, através de uma pesquisa bibliográfica nas bases de dados *Medline*, *Pubmed* e *Scielo*, usando palavras-chave relevantes: força muscular, desempenho físico, sarcopenia e doença inflamatória intestinal. A inflamação crónica é atualmente citada como um fator determinante no desenvolvimento de atrofia muscular nos casos de doença inflamatória intestinal. Além disso, o declínio de força em indivíduos com doença inflamatória intestinal, também pode ser influenciado pelas alterações na composição corporal e pela disbiose instestinal. Indicadores de força muscular e de desempenho físico devem ser considerados na identificação inicial de sarcopenia, principalmente em indivíduos com doença inflamatória intestinal, para que uma intervenção precoce possa ocorrer. A presença de citocinas pró-inflamatórias, elevada adiposidade corporal, má absorção intestinal com consequente déficit de macro e micronutrientes, perda de massa muscular e disbiose intestinal poderão ser os principais fatores com impacto na força muscular, que provavelmente medeiam a relação entre doença inflamatória intestinal e sarcopenia.

Palavras-chave – Doença inflamatória intestinal; qualidade muscular; força muscular; performance física; sarcopenia.

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