ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20221606

Factors associated with low skeletal muscle index among patients with Crohn's disease

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SUMMARY

OBJECTIVE: Disease-related skeletal muscle loss is highly prevalent among patients with Crohn's disease. Low skeletal muscle mass lead to disability and interventions to prevent skeletal mass loss as an effective strategy to prevent disability. The aim of this article was to identify the factor associated with skeletal muscle loss of Crohn's disease and seek for management target for the prevention of sarcopenia-related disability.

METHODS: Patients with Crohn's disease were divided into low and normal skeletal muscle mass groups based on L3 skeletal muscle index using abdominal CT scans. The clinical and laboratory parameters and colonoscopy were compared between the two groups. Univariate and multivariate regression logistic models were built to identify the prognostic markers of Crohn's disease-associated muscle loss.

RESULTS: A total of 191 Crohn's disease patients were enrolled in this study, of whom 116 (60.73%) were detected to have low L3 skeletal muscle index, including 71 (68.26%) males. The multivariate logistic regression analysis showed that age (OR: 1.031, 95%CI: 1.006–1.057), female gender (OR: 2.939, 95%CI: 1.386–6.233), disease duration (OR: 0.988, 95%CI: 0.980–0.996), endoscopic disease activity (simple endoscopic score for Crohn's disease) (OR: 0.923, 95%CI: 0.855–0.996), serum albumin (OR: 1.079, 95%CI: 1.009–1.154), and serum creatinine (OR: 1.037, 95%CI: 1.011–1.063) were associated with L3 skeletal muscle index among Crohn's disease patients.

CONCLUSION: The gender, age, and duration of disease were uncontrollable factors associated with muscle loss of Crohn's disease. The treatment target of mucosal healing and improved nutritional status may be beneficial for maintaining muscle mass among Crohn's disease patients.

KEYWORDS: Crohn's disease. Sarcopenia. Body composition. Endoscopy.

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by chronic, relapsing, systemic inflammation of the gastrointestinal tract, complex gastrointestinal symptoms, extraintestinal manifestations, and comorbidities[1]. The bone and skeletal muscle are vulnerable to be affected by the disease. Low muscle mass has been proven to be associated with adverse outcomes including the severity of CD, the presence of surgery related to CD, increase in the intestinal surgery-associated complications, and death[2,3]. CT is considered the gold standard technique for the detection of muscle quality and accurate assessment of body composition in patients with CD[4]. When considering only the low muscle mass based on CT or MRI, 31–61.4% of CD patients were complicated with sarcopenia[5]. The data showed that the prevalence, incidence, years of life lived with disability (YLDs), and disability-adjusted life years (DALYs) of IBD had increased in China over the past three decades. Focus on muscle loss prevention may be an important policy to manage CD-related disability[6].

Multiple factors are involved in the muscle dysfunction and sarcopenia of IBD, such as poor nutrition, physical inactivity, hormonal changes, prolonged corticosteroid therapy, high degree of lipid peroxidation or oxidative stress, and muscle protein synthesis pathways[7]. The aim of this article was to identify the controllable factors associated with skeletal muscle in the context of CD. We establish the relationship between the clinical and laboratory parameters and the skeletal muscle mass in the active stage of disease in order to seek for management target for the prevention of sarcopenia-related disability.

METHODS

Patient selection

This is a single-center retrospective study of CD data collected from the Affiliated Hospital of Yangzhou University, a Chinese tertiary teaching hospital, between January 2013 and August 2020. Hospitalized patients were consecutively enrolled in the

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was supported by the "Madical Innovation Tranformation Special Fund - New Medical Cross Innovation Team" Project of Yangzhou University, Grant number: AHYZUCXTD 202107; and the Elderly Health Research Project of Jiangsu Province, Grant number: LKM2022024.
Received on January 24, 2023. Accepted on March 28, 2023.

study with a confirmed diagnosis of CD. The inclusion criteria were as follows[1]: age ≥14 years and[2] all patients who underwent abdominal CT scan within 2 weeks before or after admission and colonoscopy during hospitalization. The exclusion criteria were as follows[1]: re-admission after recruitment and[2] clinical data or laboratory information unavailable.

Assessment of muscle mass on CT

The L3SMA measurement was done on CT images using Picture Archiving and Communication Systems (PACS, IMPAX6.3.1.4095, AGFA HealthCare NV, Belgium). The L3 skeletal muscle index (L3 SMI) is denoted by L3SMA (cm^2)/height^2 (m^2). The diagnostic criteria of low L3SMI are below 42 cm^2/m^2 for men and below 38 cm^2/m^2 for women[8].

Study design and data collection

All patients were divided into two groups, i.e., low L3SMI group and normal L3SMI based on the cutoff value of L3SMI. Clinical parameters included disease duration, the Montreal classification of CD[9], main symptoms of hospital admissions, simple Cohn's disease activity index (simple CDAI), simple endoscopic score for CD (SES-CD)[10], and treatments during hospitalization. The nutritional assessments used nutritional risk screening (NRS2002) and prognostic nutritional index (PNI). Laboratory parameters included blood cell count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, and serum levels of calcium, albumin, prealbumin, cholinesterase, creatinine, urea, and retinol-binding protein.

Ethical approval

This study was performed in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The Human Research Ethics Committee of the Affiliated Hospital of Yangzhou University approved this retrospective trial.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY, USA). All demographic, clinical, and laboratory characteristics were compared between the two groups. Normal distribution test of quantitative variables used the Shapiro-Wilk test. Normally distributed variables were described as mean± standard deviation, using an independent-samples t-test. Non-normally distributed variables were described as the median and interquartile range (IQR) using the Mann-Whitney U test. The qualitative variables were described as numbers (percentages) using the chi-square test. Univariate and multivariate regression logistic models were built to identify the prognostic markers of CD-associated muscle loss. The Pearson correlation analysis was conducted between clinical and laboratory parameters. Two-tailed $p<0.05$ was considered to be statistically significant.

RESULTS

Demographic characteristics between groups

A total of 191 CD patients were enrolled in this study, including 104 males (54.45%). The average age of patients was 40 years. A total of 116 (60.73%) patients were detected to have low L3SMI, including 71 (68.26%) males.

Clinical characteristics between groups

The duration of disease was longer in the low skeletal muscle group, but there was no statistical significance in the univariate analysis. Patients with low L3SMI had higher disease activity disease severity scores and endoscopic lesions severity scores. The simple CDAI was 5.00 (IQR: 4.00, 6.00) vs. 4.00 (IQR: 3.00, 5.00), and the SES-CD was 6.00 (IQR: 3.00, 9.75) vs. 3.00 (IQR: 0.00,6.00) (all p-values<0.01) (Table 1).

Laboratory parameters between groups

Hemoglobin and serum levels of calcium, albumin, prealbumin, retinol-binding protein, cholinesterase, creatinine, urea, and creatinine/cystatin C were significantly lower in the low L3SMI group than those in the normal L3SMI group. PLR as a systemic inflammatory marker was higher in the low L3SMI group (Table 2).

Factors associated with Crohn's disease-associated low skeletal muscle mass

Age, gender, disease duration, endoscopic activity, and serum levels of albumin, urea, and creatinine were associated with L3SMI based on univariate analysis. After multivariate regression, female gender, younger age, longer disease duration, SES-CD, and lower levels of serum albumin and serum creatinine were more likely to be diagnosed with low L3SMI (Table 3).

DISCUSSION

In this study, muscle loss diagnosed by the low L3SMI was highly prevalent among CD patients. A total of 60.73% patients had decreased skeletal muscle mass, including 71 (68.26%) males. This was in line with the previous research of Zhang et al.[2] using the same diagnostic criteria among adult Chinese patients with CD. Skeletal muscle loss showed sex-specific variations. Male patients were more prone to muscle loss in the context of CD.

Table 1. Clinical characteristics of Crohn's disease patients between the low and normal L3 skeletal muscle index groups.

Clinical parameters	All patients (n=191)	Low L3SMI (n=116)	Normal L3SMI (n=75)	p-value
Age (years)	40.00 (28.00, 50.00)	38.50 (27.00, 53.00)	40 (31.00, 53.00)	0.070
< 18	12 (6.28%)	10 (8.62%)	2 (2.70%)	
18–59	154 (80.63%)	96 (82.76%)	58 (73.33%)	
>60	25 (13.09%)	10 (8.62%)	15 (20.00%)	
Gender (n, %)				
Male	104 (54.45%)	71 (61.20%)	33 (44.00%)	0.026*
Female	87 (45.55%)	45 (38.80%)	42 (56.00%)	
Disease duration (months)	36.00 (10.00, 84.00)	36.00 (6.00, 84.00)	24.00 (6.00, 72.00)	0.078
Age at diagnosis of CD (n, %)				
A1	12 (6.28%)	10 (8.62%)	2 (2.70%)	0.125
A2	105 (54.97%)	66 (56.90%)	39 (52.00%)	
A3	74 (38.74%)	40 (34.48%)	34 (45.30%)	
Behavior of CD (n, %)				
B1	103 (53.93%)	57 (49.14%)	46 (61.33%)	0.100
B2	57 (29.84%)	36 (31.03%)	21 (28.00%)	
B3	19 (9.95%)	12 (10.34%)	7 (9.33%)	
B2+B3	12 (6.28%)	11 (9.48%)	1 (1.33%)	
Cause of hospital admission (n)				
Abdominal pain (yes/no)	163/28	101/15	62/13	0.410
Diarrhea (≥times/day) (yes/no)	32/159	21/95	11/64	0.560
Fever (yes/no)	105/86	61/55	44/31	0.458
Bloody stool (yes/no)	24/167	13/103	11/64	0.508
Disease activity (simple CDAI)	4.92 (3.00, 6.00)	5.00 (4.00, 6.00)	4.00 (3.00, 5.00)	0.003*
Endoscopic disease activity (SES-CD)	5.92 (0.00, 8.00)	6.00 (3.00, 9.75)	3.00 (0.00, 6.00)	0.001*
BMI (kg/m^2)	21.00±3.06	20.89±2.91	21.18±3.30	0.521
NRS2002	1.88 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (0.00, 3.00)	0.303
PNI	45.56±6.31	44.64±6.83	46.99±9.47	0.051
Treatments during hospitalization, (n)				
Aminosalicylic acid (yes/no)	28/163	13/103	15/60	0.099
Thiopurinen (yes/no)	51/140	29/87	22/53	0.509
Corticosteroids (yes/no)	25/166	18/98	7/68	0.274
Anti-TNF (yes/no)	39/152	27/89	12/63	0.272
Enteral nutrition (yes/no)	80/111	54/62	26/49	0.012*

*Two-tailed p<0.05 was considered to be statistically significant. CDAI: Cohn's disease activity index; SES-CD: simple endoscopic ore for Crohn's disease; PNI: prognostic nutritional index.

Previous research had suggested that muscle loss was higher in males than females[11]. Sarcopenia was considered to be an age-related disease[2]. However, for CD patients with disease-related muscle loss, there was no statistical difference in age between the low and normal skeletal muscle groups. The high prevalence of skeletal muscle loss among adolescent CD patients was partially associated with the growth impairment caused by chronic intestinal inflammation and chronic caloric insufficiency. Younger IBD patients were prone to have active inflammation, with profound malnutrition and immunosuppression[12].

Table 2. Laboratory parameter of Crohn's disease between low and normal L3 skeletal muscle index groups.

Laboratory parameters	All patients (n=191)	Low L3SMI (n=116)	Normal L3SMI (n=75)	p-value
White blood cells (10^9/L)	5.96±2.64	5.89±2.68	6.07±2.59	0.647
Neutrophils (10^9/L)	4.02±2.33	4.04±2.40	3.99±2.23	0.882
Lymphocytes (10^9/L)	1.34±0.63	1.28±0.65	1.44±0.60	0.094
Eosinophils (10^9/L)	0.12±0.13	0.12±0.14	0.12±0.12	0.981
Hemoglobin (g/L)	123.58±22.46	117.27±17.80	133.34±25.38	<0.001*
Platelets (10^9/L)	233.00 (180.50, 297.50)	240.00 (178.75, 332.75)	229.00 (188.00, 261.00)	0.193
NLR	3.84±4.10	4.10±4.64	3.44±3.44	0.285
PLR	181.60 (125.50, 269.45)	206.10 (137.89, 354.62)	146.02 (111.76, 217.88)	0.006*
ESR (mm/h)	14.00 (5.50, 29.00)	16.50 (8.75, 40.25)	12.00 (5.00, 27.00)	0.064
CRP (mg/L)	3.60 (0.62, 20.78)	6.57 (0.54, 52.63)	6.04 (0.81,17.71)	0.466
D-Dimer (mg/L)	0.26 (0.12, 0.42)	0.26 (0.14, 0.39)	0.25 (0.10, 0.49)	0.415
Serum calcium (mmol/L)	2.32±0.21	2.29±0.24	2.36±0.17	0.017*
Serum albumin (g/L)	39.30±5.70	38.26±5.34	40.97±5.92	0.001*
Serum prealbumin (g/L)	222.80±68.66	204.23±65.65	252.99±62.90	<0.001*
Serum retinol-binding protein (g/L)	36.72±16.21	33.66±14.95	41.60±17.05	0.002*
Serum cholinesterase (μ/L)	7192.06±1929.63	6746.36±1761.80	7897.74±1984.42	<0.001*
Serum creatinine (μmol/L)	62.32±19.44	57.61±17.31	69.77±20.38	<0.001*
Serum urea (mmol/L)	4.43±2.01	3.98±1.89	5.14±2.00	<0.001*
Serum cystatin C (mg/L)	0.79±0.29	0.76±0.21	0.82±0.36	0.192
Serum creatinine/cystatin C	83.08±29.98	78.88±32.08	89.78±25.10	0.020*

NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; ESR: erythrocyte sedimentation rate. *Two-tailed p<0.05 was considered to be statistically significant.

Table 3. Univariate and multivariate logistic analysis of predictor on Crohn's disease-associated muscle loss.

Variable	HR	95%CI	p-value	OR	95%CI	p-value
	Univariate analysis			Multivariate analysis		
Gender (female)	4.204	1.555–11.366	0.005*	2.939	1.386–6.233	0.005*
Age (years)	0.965	0.935–0.996	0.027*	1.031	1.006–1.057	0.016*
Disease duration (months)	1.011	1.001–1.021	0.028*	0.988	0.980–0.996	0.003*
Disease activity (simple CDAI)	1.083	0.868–1.351	0.480			
Endoscopic activity (SES-CD)	1.086	0.989–1.192	0.044*	0.923	0.855–0.996	0.040*
PNI	0.962	0.924–1.001	0.055	1.082	0.966–1.212	0.174
Lymphocyte (10^9/L)	0.936	0.399–2.196	0.880			
Hemoglobin (g/L)	0.976	0.944–1.009	0.157			
PLR	1.003	0.999–1.008	0.128			
ESR (mm/h)	0.992	0.975–1.010	0.382			
Serum albumin (g/L)	1.128	0.991–1.285	0.069	1.079	1.009–1.154	0.027*
Serum prealbumin (g/L)	0.991	0.979–1.002	0.116			
Serum cholinesterase (μ/L)	1.000	0.999–1.000	0.101			
Serum calcium (mmol/L)	0.252	0.033–1.954	0.187			
Serum urea (mmol/L)	0.723	0.527–0.993	0.045*	1.255	0.998–1.579	0.052
Serum creatinine (μmol/L)	0.936	0.892–0.981	0.006*	1.037	1.011–1.063	0.005*
Serum retinol-binding protein (g/L)	1.018	0.977–1.061	0.384			
Creatinine/cystatin C	1.000	0.983–1.018	0.990			

The variables with p<0.100 were calculated by logistic regression. *Two-tailed p<0.05 was considered to be statistically significant. PLR: platelet–lymphocyte ratio; ESR: erythrocyte sedimentation rate; PNI: prognostic nutritional index.

The CD-associated skeletal muscle loss was largely related to the duration of disease and the severity of disease activity, especially endoscopic disease activity. In our study, disease duration and SES-CD were independently associated with low L3SMI. The chronic, relapsing, persistent systemic inflammation increased disease severity with complications, longstanding active disease, and disease affecting small bowel absorption leading to CD-associated muscle loss[12]. Endoscopic disease activity may contribute to the development of malnutrition and sarcopenia by the mechanisms of malabsorption, enteric nutrient loss, and reduced energy intake due to disease manifestations[13]. Endoscopic disease activity was associated with high-level inflammation markers (such as NLR, PLR, and CRP) and poor nutrition markers (such as serum albumin, prealbumin, hemoglobin, and PNI). Thus, inflammation and nutrition play important roles in the occurrence and development of sarcopenia. This means that the primary treatment target of endoscopic healing in CD may be a benefit for the disease-related skeletal muscle loss.

Malnutrition was a highly prevalent complication in patients with IBD driven to bad outcomes. It was considered to be a principal mechanism involved in the genesis of sarcopenia[14]. During the malnutrition screening of NRS2002 and PNI, there was no significant difference between the two groups, partially because current malnutrition screening tools do not incorporate IBD-specific characteristics such as physician global assessment, steroid therapy, and endoscopic disease activity. These tools were considered to be less adequate for screening malnutritional CD patients[13]. The common nutritional status markers including albumin, prealbumin, retinol-binding protein, and cholinesterase were significantly reduced in low muscle mass patients. Notably, serum albumin independently predicts the low muscle mass of CD patients.

We established the relationship between the clinical and laboratory factors and CD-related skeletal muscle loss in order to provide evidence for the effective prevention of CD-related skeletal muscle loss. Meanwhile, the limitations were obvious. First, this is a single-center retrospective study. Patients in the study cannot be complete homogeneous. Second, the disease manifestations and complications were complex, and the skeletal muscle mass of patients was changeable during the acute and remission stages of the disease. We enrolled the first admission of patients with an acute attack of the disease during the study and were unable to discern the skeletal muscle dynamics in the disease.

In conclusion, the factors that affected CD-related muscle loss were complex and multifaceted. The gender, age, and duration of the disease were uncontrollable factors. The treatment target of mucosal healing and improved nutritional status may be beneficial for maintaining muscle mass. We initially discussed the skeletal muscle metabolic markers based on laboratory parameters. Impaired skeletal muscle synthesis rather than muscle catabolism is associated with skeletal muscle mass among CD patients, but further research is needed.

AUTHORS' CONTRIBUTIONS

JZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing–original draft, Writing –review & editing. **BJ:** Data curation, Formal Analysis, Methodology, Writing – review & editing. **SQ:** Data curation, Formal Analysis, Investigation, Project administration, Writing – review & editing. **LL:** Data curation, Formal Analysis, Supervision, Project administration, Writing – review & editing. These authors contributed equally to this article.

REFERENCES

1. Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot JF, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. Lancet Gastroenterol Hepatol. 2019;4(8):643-54. https://doi.org/10.1016/S2468-1253(19)30173-6
2. Zhang C, Yu D, Hong L, Zhang T, Liu H, Fan R, et al. Prevalence of sarcopenia and its effect on postoperative complications in patients with Crohn's disease. Gastroenterol Res Pract. 2021;2021:3267201. https://doi.org/10.1155/2021/3267201
3. Yasueda A, Sekido Y, Takeda T, Ogino T, Miyoshi N, Takahashi H, et al. Sarcopenia hinders the decline in disease activity after surgery for people with Crohn's disease: preliminary results. Nutrition. 2022;94:111526. https://doi.org/10.1016/j.nut.2021.111526
4. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006. https://doi.org/10.1139/H08-075
5. Palmese F, Del Toro R, Marzio G, Cataleta P, Sama MG, Domenicali M. Sarcopenia and vitamin D deficiency in patients with Crohn's disease: pathological conditions that should be linked together. Nutrients. 2021;13(4):1378. https://doi.org/10.3390/nu13041378
6. Qiu Y, Ren W, Liu Y, Chen WE, Pan XH, Ren JJ. Disease burden of inflammatory bowel disease in China from 1990 to 2017: findings from the global burden of diseases 2017. EClinicalMedicine. 2020;27:100544. https://doi.org/10.1016/j.eclinm.2020.100544
7. van Langenberg DR, Della Gatta P, Warmington SA, Kidgell DJ, Gibson PR, Russell AP. Objectively measured muscle fatigue in Crohn's disease: correlation with self-reported fatigue and associated factors for clinical application. J Crohns Colitis. 2014;8(2):137-46. https://doi.org/10.1016/j.crohns.2013.07.006
8. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver

disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res. 2016;46(10):951-63. https://doi.org/10.1111/hepr.12774

9. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53. https://doi.org/10.1136/gut.2005.082909
10. Daperno M, D'Haens G, Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505-12. https://doi.org/10.1016/s0016-5107(04)01878-4
11. Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr. 2014;68(9):1001-7. https://doi.org/10.1038/ejcn.2014.117
12. Ryan E, McNicholas D, Creavin B, Kelly ME, Walsh T, Beddy D. Sarcopenia and inflammatory bowel disease: a systematic review. Inflamm Bowel Dis. 2019;25(1):67-73. https://doi.org/10.1093/ibd/izy212
13. Einav L, Hirsch A, Ron Y, Cohen NA, Lahav S, Kornblum J, et al. Risk factors for malnutrition among IBD patients. Nutrients. 2021;13(11):4098. https://doi.org/10.3390/nu13114098
14. Ünal NG, Oruç N, Tomey O, Ömer Özütemiz A. Malnutrition and sarcopenia are prevalent among inflammatory bowel disease patients with clinical remission. Eur J Gastroenterol Hepatol. 2021;33(11):1367-75. https://doi.org/10.1097/MEG.0000000000002044