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RESEARCH ARTICLE

Assessment of Sarcopenia as an Independent Nutritional Indicator in Pediatric Inflammatory Bowel Disease

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Abstract:

Objective: To evaluate the presence of sarcopenia in a cohort of patients with pediatric inflammatory bowel disease (pIBD) and compare it to the presence of malnutrition according to body mass index (BMI).

Methods: Descriptive study of patients between 1-16 years of age with IBD who underwent magnetic resonance enterography (MRE) between June 2018 and June 2022, followed at a University Hospital in Argentina. Clinical characteristics and anthropometric data were collected, and BMI and standard deviations were calculated. Total Psoas Muscle Area (tPMA) at levels L3–4 and L4–5 was compared with pediatric age and sex-specific growth curves.

Results: We included 40 patients (50% females), 16 (40%) with Crohn's disease, and 24 (60%) with ulcerative colitis, mean age 9 years (IQR 3-13). The median time to MRE was 3 months after diagnosis (IQR 33 days- 1.5 years). In our cohort, 40% of patients had tPMA below the 5th percentile (z score -2). In contrast, only 3 patients (7.5%) had a BMI z score $<$ -2. During follow-up, there was no significant difference in the use of biologics or number of relapses between patients with and without sarcopenia.

Conclusions: Our cohort of pIBD had lower muscle mass even in the short term. Our data show that sarcopenia can also be present despite a normal BMI. This finding reinforces the idea that sarcopenia could be an anthropometry-independent indicator of nutritional status and frailty in pIBD.

Keywords: Muscle-mass, Cross-sectional imaging, Frailty

Introduction

Unlike adult-onset inflammatory bowel disease (IBD), the impact of IBD on nutritional status and consequently on the child's growth is of major importance in pediatric inflammatory bowel disease (pIBD). Linear growth impairment is common at the time of diagnosis of pIBD, especially in Crohn's disease (CD), and growth may be impaired even before the onset of significant gastrointestinal symptoms [1]. The impact of the patient's nutritional status is of such relevance in CD that already since 2014 international guidelines have considered growth retardation as a poor prognostic factor and an indication for biological treatment [2].

Weight and height were recorded, and body mass index (BMI) was calculated. Each one of the above captures a different dimension of growth but, although each one is important, none by themself is sufficient to adequately describe a child's nutritional status [3]. Analytic morphomics, such as psoas muscle area, trabecular bone density, and visceral fat area by age and sex has superior clinical utility and accuracy in risk stratification than traditional factors such as age, height, and weight [4].

Sarcopenia refers to the loss of skeletal muscle mass and strength [3,5,6], which often accompanies the normal aging process but can also occur in chronic medical conditions. Sarcopenia is proposed as a new nutritional index that implies a measure of frailty, a state of severe risk, and great vulnerability in seniors and patients with chronic pathologies. Sarcopenia is highly prevalent in adults with IBD in clinical remission (up to 60%) [7] and is associated with disease activity, need for salvage therapy, postoperative complications after bowel resection, and colectomy in patients with severe acute colitis [8-10]. However, sarcopenia is not a problem unique to adults. Children with chronic diseases suffer from nutritional deficiencies, physical deconditioning, and systemic inflammation that may contribute to involuntary muscle loss [11]. There are studies in the pediatric population that have established reference values for sarcopenia such as those by Lurz [11], Harbaugh [4], Marunowski [12] and Metzger [13], which differ in the parameters assessed as well as the population studied. Unfortunately, no reference values are available in Latin America to date. Nevertheless, a study performed in Argentina in children with end-stage liver disease and extrahepatic portal hypertension found the psoas muscle area status was affected in all hepatic patients without correlation with BMI [14] .

There is currently scarce data on the prevalence of sarcopenia in pIBD, and whether there are relationships with other nutritional parameters such as low BMI.

Objective

To evaluate the existence of sarcopenia in a cohort of patients with pIBD and compare it with the presence of malnutrition diagnosed by BMI.

Methods

A single-center, retrospective study of a cohort of patients between 1-16 of age with IBD was performed. Patients were followed at a University Hospital in Buenos Aires, Argentina, a referral center for pIBD, with more than 30 years of experience and over 300 patients taken care of. Patients aged 1-16 years diagnosed with IBD according to the Porto criteria [15] who underwent magnetic resonance enterography (MRE) between June 2018 and June 2022 were included. The revised Porto criteria identify subtypes of pIBD: ulcerative colitis (UC), atypical UC, IBD unclassified , and CD. These criteria recommend upper gastrointestinal endoscopy and ileocolonoscopy for all suspected patients with pIBD, with small bowel imaging by MRE or wireless capsule endoscopy [15].

Patients with comorbidities such as renal or liver transplant, affecting nutritional status and/or bone metabolism, growth, or pubertal development were excluded. Medical records were reviewed by a pediatric gastroenterologist (MSA). MRE scans were retrieved from the institution's Imaging Archive and Communication System. Sarcopenia was assessed by two independent senior radiologists (CD and TK). Total psoas muscle area (tPMA) at the L3-4 and L4-5 levels was calculated by adding the left and right PMA and expressed as square millimeters (mm2). Results were compared with age- and sex-specific pediatric reference values of tPMA at the L3-4 and L4-5 intervertebral levels for children between 1 and 16 years of age [11]. Data was entered into a spreadsheet in a codified manner to protect privacy. Demographic and clinical characteristics were documented. Recorded at the time of the MRE were sex, disease classification, age at diagnosis, disease location and clinical course, according to PCDAI scores [16] / PUCAI [17], anthropometrics (weight, height, BMI), and z- scores according to World Health Organization (WHO) growth charts [18], laboratory parameters (fecal calprotectin (FC), albumin, C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), and treatment.

PCDAI and PUCAI are noninvasive and valid indexes to assess disease activity in pediatric CD and UC respectively.

Reference values used were those published by Lurz et al [11], performed in healthy children with a history of trauma in whom abdominal cross-sectional imaging by computed tomography (CT) had been performed. This study was chosen because, unlike other published studies, values are provided in an easily accessible virtual calculator allowing exact z-score values to be obtained.

Statistical analysis

Quantitative data are expressed as median and interquartile range (IQR) (25-75). Qualitative data are presented as absolute and relative frequencies. Mann-Whitney U test was used for quantitative data comparisons, while the Chi-squared test was employed for qualitative data. The correlation between BMI and sarcopenia z-scores was assessed using Spearman's rank correlation. A significance level of less than 5% was considered statistically significant. The analysis was performed using R software version 4.2.3. The study was approved by the Medical Ethics Committee of the Hospital Italiano.

Results

A total of 40 patients with pIBD were included. The cohort's median age was 9 years (IQR 3-13). The median time to MRE was 3 months after diagnosis (IQR 33 days-1.5 years). In those patients in whom the MRE was performed within 3 months of diagnosis, there was a higher prevalence of sarcopenia (55%) than in those in whom it was performed after 3 months (25%) (p 0.107). Sarcopenia was diagnosed in 40% of the patients with a tPMA below the 5th percentile (z score < -2). Of 37 subjects with BMI z-score > -2, 23 (62%) were sarcopenic. Of those with a BMI z-score < -2, only 33% were sarcopenic (Figures 1 and 2). In patients with sarcopenia, a BMI z-score of < -2 had a positive predictive value of 66.7 and in those with a BMI z-score > -2, a negative predictive value of 62.7. There were no patients with a BMI greater than the 90th percentile (obesity). Analysis of baseline characteristics and risk factors associated with sarcopenia are shown in Tables 1 and 2.

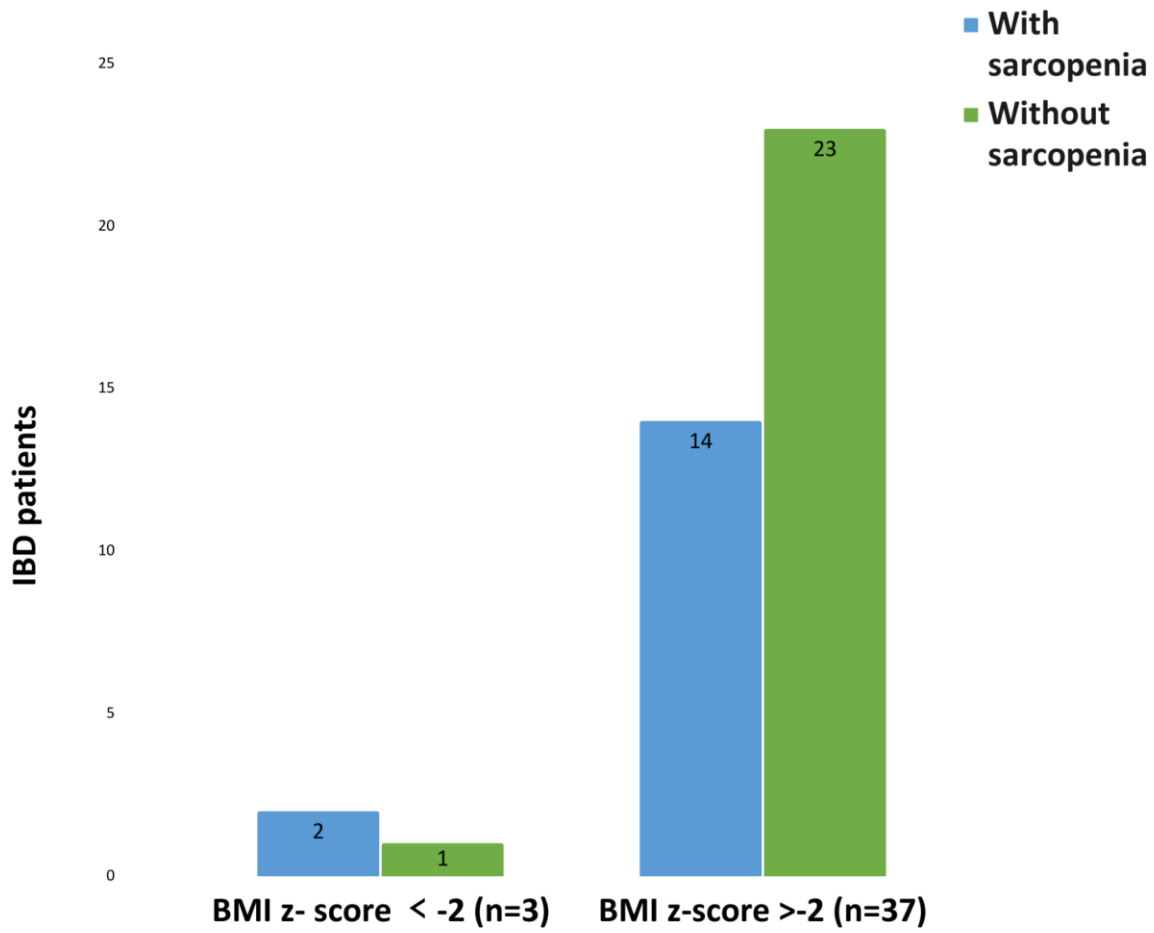

Figure 1: Correlation between sarcopenia and body mass index (BMI)
IBD: Inflammatory Bowel Disease, BMI: body mass index

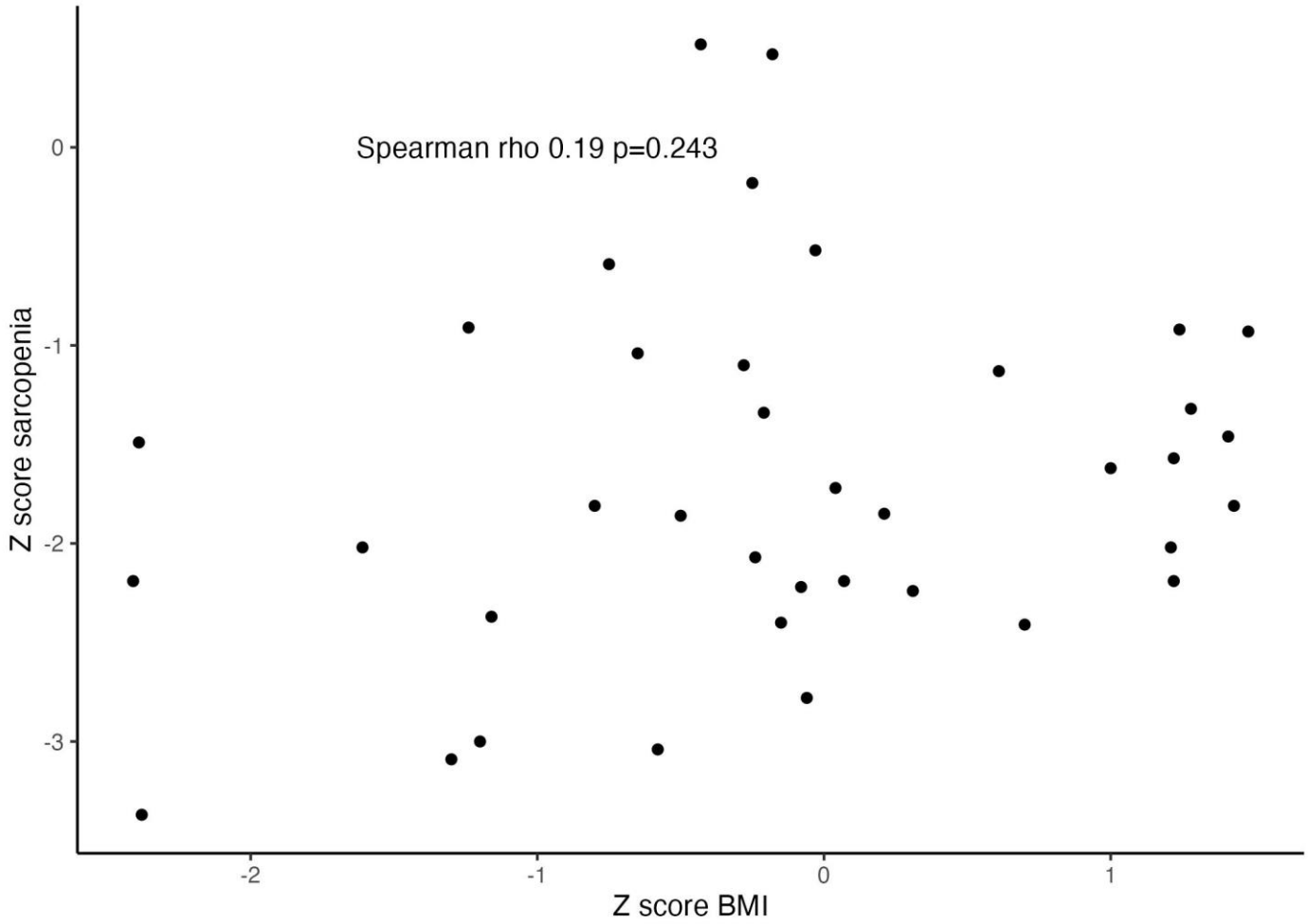

Figure 2: Scatterplot of Total Psoas Muscle Area (tPMA) and body mass index (BMI) z-scores
Median z- score tPMA -1.8 (IQR -2.2; -1.1); Median z-score BMI -0.1 (IQR -0.7; 0-7)

Table 1 - Baseline patient characteristics

n: 40

Female n (%)	20 (50%)
Disease	
***UC** n (%)*	24(60%)
UC E4 n (%)	22(92%)
PUCAI n (%)	
0: remision	4 (17%)
1: mild	8 (33%)
2:moderate	10 (42%)

3: severe	2 (8%)
***CD** n(%)*	16(40%)
Panenteric CrD n (%)	9 (56%)
CrD B1	14(88%)
PCDAI n (%)	
0: remision	3 (19 %)
1: mild	6(38%)
2:moderate	5(31%)
3: severe	2(12%)
z-score BMI(kg/m²) median [IQR]	-0.07 [-0.68, 0.7]
Laboratory	
ESR (mm/h) median [IQR]	21.5 [9, 29.8]
CRP (mg/l) median [IQR]	1.1 [0.2, 4.23]
Albumin(g/dl) median [IQR]	3.96 [3.5, 4.28]
*FC (*ug/g) *median* [IQR]	751 [386.8, 1000]
IBD Therapy	
5-ASA n (%)	38 (95.0)
Immunomodulator n (%)	15 (37.5%)
Corticosteroids n (%)	24 (60.0)
Biologic agents n (%)	5(12.5%)

CD: Crohn's disease, UC: ulcerative colitis, E4:Pancolitis (proximal to hepatic flexure), PCDAI: Pediatric Crohn's Disease Activity Index, PUCAI: Pediatric Ulcerative Colitis Activity Index, B1: non stricturing non-penetrating, BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, FC: fecal calprotectin, IBD: inflammatory bowel disease, 5-ASA: 5- aminosalicylic acid

Table 2- Risk factors for sarcopenia

Sarcopenia **Z score < - 2**	**YES**	**NO**	**p value**
	16(40%)	24 (60%)	
Female n (%)	7(43.8%)	13(54.2%)	0.747
UC	9(56.2%)	15(62.5%)	0.947
CD	7(43.8%)	9(37.5%)	
Panenteric CD n (%)	4(57%)	5(33.3%)	1
CD B1	6(85%)	8(89%)	1
UC E4	8(89%)	14(93%)	
PCDAI/PUCAI n (%)			0.392/0.279
0: remision	1	6	
1: mild	8	6	
2:moderate	5	10	
3: severe	2	2	
z-score BMI(kg/m²) median [IQR]	-0.20 [-1.22, 0.13]	0.12 [-0.34, 1.23]	0.062
Laboratory			
ESR (mm/h)*median* [IQR]	25.50 [13.25, 39.00]	16.00 [8.00, 24.25]	0,109
CRP (mg/l) *median* [IQR]	0.85 [0.20, 8.68]	1.60 [0.27, 4.12]	0.923
*Albumin(*g/dl) *median* [IQR]	3.81 [3.42, 3.99]	4.02 [3.66, 4.58]	0.109
*FC (*ug/g) *median* [IQR]	732.50 [395.50, 924.25]	767.50 [334.75, 1000]	0.967
IBD Therapy			
Corticosteroids n (%)	7(43.8%)	17(70.8%)	0.11
Biologic agents n (%)	2(12.5%)	3(12.5%)	1
Time since diagnosis			
(months)*median* [IQR]	1.53 [0.32, 15.15]	4.53 [2.43, 14.73]	0.102

CD: Crohn's disease, UC: ulcerative colitis, PCDAI: Pediatric Crohn's Disease Activity Index, PUCAI: Pediatric Ulcerative Colitis Activity Index, BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, FC: fecal calprotectin, IBD: inflammatory bowel disease

We had follow-up in 36 (90%) patients. The mean follow-up length was 2.8 years. No significant differences were observed between patients with and without sarcopenia regarding the number of relapses (p 0.69) or need for steroids (p 0.123). In terms of the use of biologics, 12 patients (80%) with sarcopenia needed biologic treatment during follow-up while 14 patients without sarcopenia (67%) did not require them (p 0.615). Only 5 patients (12.5%) in the cohort had a repeat MRE during follow-up. Three of them remained without sarcopenia at the second MRE; the remaining two who had sarcopenia in the first study, still had it.

Discussion

Few publications address sarcopenia in pIBD and, to the best of our knowledge, this is the first one from Latin America. We demonstrate that children and adolescents with pIBD have lower muscle mass than reference values, with more than 40% of our patients being below the 5th percentile (z score $<$ -2). This has also been observed in short-term disease duration, as most of the MRE were performed as part of the initial diagnostic work-up of IBD. It can be speculated that a prolonged, albeit silent, inflammatory process preceded the diagnosis and was responsible for the loss of muscle mass. On the other hand, in our cohort, 25% of the patients who underwent MRE had already been diagnosed with IBD more than 18 months prior. Although it could be expected that sarcopenia would improve with treatment over time, most of these patients had not yet received treatment with biologics, an approach that has modified the natural course of the disease.

Regarding one of the risk parameters classically associated with sarcopenia such as low albumin [10,19], in our patients albumin was within normal range. Similar results have been found in a study performed in Israel in patients with pIBD by Atlan et al. [19]. Moreover, in our patients, sarcopenia was present with an unchanged BMI. This reinforces the idea that sarcopenia seems to be an anthropometry-independent indicator of nutritional status, at least in our patients.

Regarding disease activity, most of our patients with sarcopenia at the time of MRE did not present severe clinical activity nor abnormal laboratory parameters other than elevated FC. This would suggest that even those patients who are clinically well may be at risk for muscle mass depletion.

Despite the short follow-up time, we found no significant differences in the number of relapses between patients with or without sarcopenia. However, more patients with sarcopenia, although this did not reach statistical significance, required escalation to biologics during the follow-up which could infer that they had a worse clinical course, like the findings of Atlan et al. [20].

Although the most common methodology used to assess body composition has been dual-energy x-ray absorptiometry, measurement of tPMA from cross-sectional abdominal CT or MRE images represents a rapid and easily accessible method for assessing the presence of sarcopenia. The psoas muscle and possibly paraspinal and abdominal wall muscles are considered core skeletal muscles, which are relatively independent of activity and fluid retention but are altered by metabolic and molecular complications of chronic disease. The reference values we used are derived from CT scans, although we measure sarcopenia by MRE. Like CT, MRE's

accuracy in the assessment of muscle cross-sectional area/volume with the segmentation of muscles on cross-sectional images is very high, with a strong correlation between the two modalities, both with old and new equipment [21,22]. As in the study by Lurz et al. [11], the measurements were performed at the same level (L3-4 and L4-5). As an additional advantage, MRE does not use radiation and being a routine exam indicated to evaluate small bowel involvement or complications of pIBD, it does not involve an additional procedure.

Recently, Marunowski et al. [12] published MRE-derived reference values of tPMA in the form of percentile charts for children aged from 1 to 18 years in a Caucasian population in Poland. In our study we chose the reference data of Lurz et al. because it presents more ethnic variability and the data can be obtained from an online application to easily calculate age-specific and sex-specific z-scores and percentiles, which yields more accurate data than percentile charts alone.

Another diagnostic tool for the measurement of sarcopenia that is increasingly used in IBD is ultrasound. Unlike the imaging techniques, it is easier to use, reproducible, does not use ionizing radiation, and is portable and readily available. However, there is no normative data on population-based scale sarcopenia, and no cut-off points for ultrasound-based diagnosis of sarcopenia [22]. The measurement and the site of measurement are different from axial cut-off techniques, therefore, results cannot be extrapolated or compared.

One of the limitations of our study is that the reference values for healthy patients come from Toronto, Canada, where there is a great ethnic diversity. As in Canada, Argentina is considered a country where migratory movements influence the ethnic composition. In Buenos Aires, almost 80% of the population are European immigrants, the remaining 20% are of Latin-American racial background, and an extremely small percentage are of African descent. In our study, we did not find patients with BMI in the obese range. This is similar to the Canadian population, unlike the other reference tables for psoas muscle area in healthy children such as that of Metzger et al. [13] where 25% of the cohort had a BMI greater than the 90th percentile.

Unfortunately, the study design did not include parameters of endoscopic severity or other radiological signs of inflammation to compare with sarcopenia that could provide a more comprehensive understanding of the relationship between muscle mass and disease activity.

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Conclusions

In this cohort of pIBD patients, we observed a lower muscle mass index, even in the short-term follow-up. Accordingly, it seems that sarcopenia can also be detected even in children with unchanged BMI. This reinforces the idea that sarcopenia can help in the workup of nutritional status and frailty as an independent anthropometry indicator. New studies with a larger number of patients and different diagnostic tools will be needed to confirm these observations and thus be able to establish future recommendations.

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