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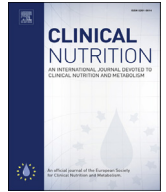
Original article

Assessment of bioelectrical phase angle as a predictor of nutritional status in patients with Crohn's disease: A cross sectional study

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SUMMARY

Background & aims: The assessment of body composition (BC) can be used to identify malnutrition in patients with Crohn's disease (CD). The aim of this study was to evaluate the nutritional status of CD patients by assessing BC, phase angle (PhA) and muscle strength. Differences in disease duration and medications were also considered.

Methods: Consecutive adult CD patients aged 18−65 years were enrolled in this cross-sectional study. Disease activity was clinically defined by the Crohn's Disease Activity Index (CDAI) in the active and quiescent phases. All participants underwent anthropometry, BC and handgrip-strength (HGS) measurements; additionally, blood samples were taken. Data from CD patients were also compared with age-, sex- and BMI-matched healthy people.

Results: A total of 140 CD patients with a mean age of 38.8 ± 13.9 years and a mean body weight of 64.9 ± 12 kg were recruited and compared to controls. The findings showed that all nutritional parameters, especially PhA and HGS, were lower in CD patients than in controls, and these parameters were substantially impaired as disease activity increased. Active CD patients had a lower body weight and fat mass than both the quiescent and control groups. PhA was negatively correlated with age ($r = -0.362$; $p = 0.000$) and CDAI ($r = -0.135$; $p = 0.001$) but was positively associated with fat free mass (FFM) ($r = 0.443$; $p = 0.000$) and HGS ($r = 0.539$; $p = 0.000$). Similarly, serum protein markers were lower in the active CD group than in the quiescent group ($p < 0.05$). Disease duration and medications did not significantly affect nutritional status.

Conclusions: BIA-derived PhA is a valid indicator of nutritional status in CD patients, and its values decreased with increasing disease activity. Additionally, small alterations in BC, such as low FFM, and reduced HGS values can be considered markers of nutritional deficiency. Therefore, the assessment of BC should be recommended in clinical practice for screening and monitoring the nutritional status of CD patients.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder involving any part of the gastro-intestinal tract and is characterized by a relapsing course [1]. Patients affected by CD have an increased risk of malnutrition due to malabsorption, diarrhea, multiple intestinal resection, inadequate food intake, enhanced nutrient requirements, anorexia, pain and vomiting [2]. Recently, the current criteria for the diagnosis of malnutrition recommend the assessment of body composition (BC) [3] since body mass index (BMI)

alone can be misleading. According to a recent systematic review, nearly one-third of CD patients had altered body composition, with reductions in both lean and fat mass, despite only 5% of them being underweight according to BMI criteria [4].

Bioelectrical impedance analysis (BIA) is a portable, easy-to-use and inexpensive method for estimating fat mass (FM) and fat-free mass (FFM) in clinical settings [5]. Specifically, BIA measures whole-body impedance, the opposition of the body to alternating current consisting of two components: resistance (R) and reactance (Xc). The most clinically relevant impedance parameter is the phase angle (PhA), an index of cell membrane integrity and vitality, which provides crucial information on cellular health and soft tissue hydration [6]. PhA, however, can be affected by several clinical conditions, including inflammation, malnutrition, and prolonged physical inactivity, resulting in its prominent reduction [7—10]. Low PhA values are usually associated with impaired muscle function, poor physical performance [5,11—13] and low survival [6,14].

Theoretically, PhA might be considered a nutritional indicator since malnutrition is characterized by alterations in fluid balance and changes in cellular membrane integrity. As such, many studies used PhA as a tool for predicting nutritional status as well as for assessing clinical results and/or disease progression in different clinical conditions [15—18]. To date, however, only a few studies [19,20] have assessed impedance parameters to identify and monitor nutritional risk in adults with CD, showing contrasting results.

CD patients can be at risk of malnutrition even when the disease appears quiescent [21] since the degree of malnutrition is strongly influenced by the activity, duration and extent of the disease and by the inflammatory response. However, the widespread use of biologic agents for CD treatment has allowed for an improved and sustained control of mucosal inflammation as well as of symptoms in a significant proportion of patients [22—26], which is expected to positively affect nutritional status.

Thus, the aims of the present study were 1) to evaluate body composition, PhA (total and segmental) and muscle strength as indicators of nutritional status in CD patients; 2) to verify the impact of clinical disease activity on nutritional and functional status; and 3) to assess whether disease duration and drug treatments could influence body composition and PhA.

2. Materials and methods

2.1. Design and study population

This cross-sectional study focused on nutritional status evaluation in patients with CD by including BIA parameters, such as PhA, and muscle strength. Adult patients with a diagnosis of CD according to the European Crohn's and Colitis Organization (ECCO) guidelines, were consecutively recruited from July 2016 until March 2018 at the Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples (Italy). The inclusion criteria were a diagnosis of CD and an age between 18 and 65 years. The exclusion criteria were as follows: use of corticosteroids in the last 3 months; history of acute or chronic liver or kidney disease; current enteral (i.e., tube feeding) or parenteral nutrition, presence of fistulae, ileostomy or colostomy; presence of extensive small bowel resections (residual small bowel < 2 m); pregnancy or lactation; unstable body weight in the last month; and unable or unwilling to give informed consent.

Additionally, data from age- sex- and BMI-matched healthy people (n = 83) were randomly selected from our database (Caucasian adults, aged between 18 and 75 years) to serve as a control group.

All measurements were performed early in the morning after a fasting period of 8—10 h according to standardized conditions, i.e., abstaining from alcohol and vigorous physical activity for 24 h prior to the assessment. Clinically, disease activity was defined by the Crohn's Disease Activity Index (CDAI), classifying patients in the active and quiescent phases ($\geq$150 and <150, respectively). Demographic data, disease duration, smoking habits, previous surgery, drug treatment and location and disease behavior (Montreal classification) were also collected. The study was conducted according to the Declaration of Helsinki and received the approval of the Federico II Ethical Committee (Protocol's number: 102/16) and was registered at clinicaltrials.gov as NCT03054935. All participants provided written informed consent prior to enrolment.

2.2. Anthropometry and bioelectrical impedance analysis

Body weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively, and were taken while the subjects wore light clothes and no shoes using a platform beam scale with a built-in stadiometer (Seca 709; Seca, Hamburg Germany). BMI was calculated as body weight expressed in kilograms divided by squared height reported in meters.

BIA [27] was performed at 50 kHz (Human In Plus II, DS Medica, Milan, Italy) with a constant room temperature of 22—25 °C. Measurements were carried out on the nondominant side of the body, in the postabsorptive state, after voiding and with the subject in the supine position for 20 min. The BIA variables considered were R and Xc, while PhA was calculated as arc tangent Xc/R x 180°/ π and expressed in degrees. For the segmental BIA exam, the length of each segment was measured, and the electrodes were properly positioned to obtain R and Xc values for each of the following segments: arm and leg. This evaluation was conducted according to the Organ method [28]. Finally, FFM and FM were estimated by using the predictive equations developed by Kushner [29].

2.3. Muscle strength measurement

Handgrip strength (HGS) measures the ability of the hand muscles to generate tension (force) through a handshake by using a dynamometer (JAMAR, Roylan, UK). Subjects were placed standing with arms outstretched parallel to the trunk and then held the dynamometer and applied maximum strength with each hand without support. The measurement was repeated three times alternately on both sides (dominant and nondominant hand) with 1 min apart to avoid fatigue; then, the mean value was recorded in kilograms (kg) [30].

2.4. Biochemical indicators

Blood samples were taken to evaluate several biomarkers involved in nutritional status, such as albumin (g/dl), hemoglobin (Hb) (g/dl), total cholesterol (mg/dl), total lymphocytes (10^{-3}/ml), prealbumin (g/L), pseudocholinesterase (UI), alpha-2 fraction (%), C-reactive protein (CRP) (mg/L), fibrinogen (mg/dl), total protein (g/ dl), transferrin (g/dl) and ferritin (ng/dl). All determinations were performed at the centralized laboratory of Federico II University Hospital following standardized techniques.

2.5. Statistical analysis

Data are presented as the mean ± standard deviation [SD], unless otherwise specified. The Kolmogorov—Smirnov Test and the Shapiro—Wilk Test were used as tests of normality to examine whether variables were normally distributed. Data were compared between the CDAI groups using an unpaired t-test, while data were

compared between CD groups and controls as well as among treatments by using one-way ANOVA with Tukey post hoc comparisons. Linear correlation was applied to evaluate associations between variables. Statistical analysis was performed using SPSS ver. 22.0 (IBM Corporation, Inc. Chicago, IL, USA). A p value < 0.05 was considered significant.

3. Results

One hundred forty-eight CD patients were recruited for this study. Six were excluded for not fulfilling the inclusion criteria, and 2 were excluded for taking corticosteroids. Therefore, a total of 140 CD patients (82 males and 58 females) were finally included in the analysis, showing a mean age of 38.8 ± 13.9 years, an average weight of 64.9 ± 12 kg and a BMI of 23.2 ± 3.72 kg/m². Based on the CDAI score, 78 patients were in the quiescent phase (CDAI< 150), while 62 showed mild to moderate disease activity (150 > CDAI < 450). All demographic and clinical characteristics of patients are shown in Table 1. Briefly, most of the participants (n = 102) had a normal weight (73%), 9 (6.4%), mainly women, were underweight and 29 (20%) were overweight/obese according to BMI criteria. The overall disease duration ranged between 0.5 and 36 years, with an average time of 9 years in both sexes, while 53% of the entire sample underwent previous surgery due to CD. Regarding smoking status, 26 patients were smokers, 22 were ex-smokers and 91 had never smoked. Based on the Montreal classification, CD was mainly diagnosed at an age between 17 and 40 years (66%), located in the ileum − colon (57%) and characterized by a stricturing phenotype (54%). Finally, regarding the use of

medications, we found that biologic agents were used in 40% of patients, followed by immunosuppressives and mesalazine treatments (17% and 12%, respectively). Surprisingly, almost 31% of patients were not being treated at the time of the study visit due to the screening phase before starting biologic therapy.

3.1. Body composition, phase angle and muscle strength

As mentioned before, a group of healthy age-, sex- and BMI-matched subjects (n = 83; 45 males and 38 females) were selected. Age, body weight, BMI, all BIA variables, including total- and segmental PhA values and muscle strength are shown for CD patients and controls in Table 2. Overall, the nutritional status of CD patients differed from that of the control group. We found that body weight, BMI, FFM and HGS as well as total and arm-PhA were significantly lower in all CD patients than in controls. A subgroup analysis was performed by splitting CD patients according to CDAI. Our findings showed that patients in the active group had a lower body weight, FM, and total and leg-PhA than both the quiescent and control groups. However, BMI, FFM and arm-PhA were different only between the active CD group and the controls. Finally, HGS did not change between the CDAI groups but significantly differed compared to that of the controls.

Next, we performed the statistical analyses taking sex differences into account, as presented in Table 3. Overall, we observed reduced values for body weight, BMI, FFM, FM (in kg), HGS and arm-PhA in male CD patients compared with the same parameters in controls. In females, we found lower FFM than in the control group, although both showed a similar BMI; furthermore, HGS as well as total- and arm-PhA values are reduced. After stratifying by CDAI, we showed that both males and females in the active group had decreased values of FM (expressed both as kg and percentage) and total and leg-PhA than those in the quiescent group. Additionally, active females had a lower body weight than those in the quiescent phase. After comparing the three groups, we observed that FFM and HGS were significantly lower in CD patients than in controls, independent of sex and CDAI. However, both FM and leg-PhA values were reduced in both male and female CD patients for the active group only.

3.2. Correlation coefficients between PhA, age, body composition and HGS

Pearson correlation coefficients for the association of total PhA with individual characteristics and all BIA variables in CD patients are shown in Table 4. We found that total PhA was negatively correlated with age (r = −0.362; p = 0.000), CDAI (r = −0.315; p = 0.000) and fat percentage (r = −0.206; p = 0.01), whereas it was positively associated with body weight (r = 0.353; p = 0.000), FFM (r = 0.443; p = 0.000) and HGS (r = 0.539; p = 0.000). Similar correlations were found in both CDAI groups, except FM (%) was not significantly associated with PhA in the active group.

For further analysis, correlations were controlled for age and sex. Again, our findings showed that total PhA was inversely correlated with CDAI (r = −0.267; p = 0.002) and positively associated with body weight (r = 0.169; p = 0.04), BMI (r = 0.240; p = 0.005), FM expressed in kg (r = 0.212; p = 0.012) and percentage (r = 0.214; p = 0.012) and HGS (r = 0.153; p = 0.05) but not with FFM (r = 0.029; p = 0.765).

Finally, HGS was correlated with segmental PhA values, showing a positive association with both arm- (r = 0.626; p = 0.000) and leg-PhA (r = 0.318; p = 0.000) values, as presented in Fig. 1, highlighting a stronger correlation of arm-PhA than that of the leg values.

Table 1
Demographic and clinical characteristics of CD patients.

	Total	Men	Women
N, (%)	140 (100)	82 (58.6)	58 (41.4)
BMI, n (%)			
<18.5 kg/m²	9 (6.4)	1 (1.2)	8 (13.8)
18.5−24.9 kg/m²	102 (72.9)	66 (80.5)	36 (62.1)
25−29.9 kg/m²	21 (15)	12 (14.6)	9 (15.5)
>30 kg/m²	8 (5.7)	3 (3.7)	5 (8.6)
Previous surgery, n (%)	74 (52.9)	41 (50.0)	33 (56.9)
Mean duration (years), y [range]	8.80 [0.5−36]	9.01 [1−30]	8.52 [0.5−36]
Currently smoking habits n (%)			
Yes	26 (18.6)	13 (15.9)	13 (22.4)
No	91 (65.0)	57 (69.5)	35 (60.3)
Ex-smoker	22 (15.8)	12 (14.6)	10 (17.2)
Clinical activity, n (%)			
CDAI < 150	78 (55.7)	50 (61)	28 (48.3)
>150 CDAI < 450	62 (44.3)	32 (39)	30 (51.7)
Montreal age at diagnosis, n (%)			
A1: <16 y	26 (18.6)	17 (20.7)	9 (15.5)
A2: 17−40 y	93 (66.4)	53 (64.6)	40 (69.0)
A3: >40 y	21 (15.0)	12 (14.6)	9 (15.5)
Montreal disease location, n (%)			
L1: Ileum	46 (32.9)	28 (34.1)	18 (31.0)
L2: Colon	11 (7.9)	10 (12.2)	1 (1.7)
L3: Ileum and colon	80 (57.1)	42 (51.2)	38 (65.5)
L4: Upper GI tract	3 (2.1)	2 (2.4)	1 (1.7)
Montreal disease behaviour, n (%)			
B1: Inflammatory	37 (26.4)	27 (32.9)	10 (17.2)
B2: Stricturing	76 (54.3)	43 (52.4)	33 (56.9)
B3: Penetrating	27 (19.3)	12 (14.6)	15 (25.9)
Perianal disease, n (%)	30 (21.4)	17 (20.7)	13 (22.4)
Medications, n (%)			
None	43 (30.7)	23 (28.0)	20 (34.5)
5-ASA	17 (12.1)	14 (17.0)	10 (17.2)
IMMs	24 (17.1)	9 (17.1)	8 (13.8)
Biologics	56 (40.0)	36 (43.9)	20 (34.5)

Body Mass Index (BMI); Crohn Disease Activity Index (CDAI); years (y); amino salicylic acid (ASA); Immunosuppressives (IMMs).

Table 2
Age, BMI, body composition, handgrip strength and phase angle measurements in all CD patients and controls.

	Active (n = 62)	Quiescent (n = 78)	p[a]	All (n = 140)	Controls (n = 83)	p[b]	p[c]
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		
Age, years	39.6 ± 14.2	38.2 ± 13.8	0.805	38.8 ± 14.0	37.5 ± 11.0	0.458	0.624
Weight, kg	61.9 ± 10.8	67.3 ± 12.5	0.034	64.9 ± 12.0	70.5 ± 13.9	0.002	0.000§
BMI, kg/m[b]	22.5 ± 3.17	23.7 ± 4.04	0.106	23.2 ± 3.72	24.2 ± 3.5	0.028	0.012§
FFM, kg	48.2 ± 10.8	50.0 ± 9.78	0.591	49.2 ± 10.2	53 ± 12.1	0.013	0.028§
FM kg	13.7 ± 6.67	17.3 ± 8.79	0.022	15.7 ± 8.10	17.5 ± 7.64	0.100	0.008§
FM, %	22.3 ± 10.2	25.2 ± 10.4	0.186	23.9 ± 10.4	24.8 ± 8.78	0.489	0.170
HGS, kg	27.6 ± 10.4	28.7 ± 10.1	0.769	28.2 ± 10.2	33.8 ± 7.97	0.000	0.000‡
Total PhA, (°)	6.07 ± 0.92	6.58 ± 0.90	0.002	6.35 ± 0.94	6.81 ± 0.79	0.000	0.000§
Arms PhA, (°)	5.46 ± 1.03	4.87 ± 0.95	0.159	4.73 ± 0.99	5.30 ± 1.02	0.000	0.000§
Legs PhA, (°)	7.18 ± 1.11	7.95 ± 1.05	0.000	7.61 ± 1.14	7.75 ± 1.34	0.433	0.001§

CDAI: Chron's Disease Activity Index; FFM: fat free mass; FM: fat mass; HGS: handgrip strength, PhA: phase angle.
[a] Un-paired T test between active vs. quiescent.
[b] Un-paired T test between All vs. controls.
[c] ANOVA test among active, quiescent and controls with significant values between: (§) active vs. controls; (‡) active and quiescent vs. controls.

Table 3
Age, BMI, body composition, phase angle and handgrip strength in all CD patients and controls according to sex.

	Active (M = 32; W = 30)	Quiescent (M = 50; W = 28)	p[a]	All (M = 82; W = 58)	Controls (M = 45; W = 38)	p[b]	p[c]
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		
Age, years							
Males	40.4 ± 13.7	36.6 ± 13.7	0.215	38.1 ± 13.8	38.2 ± 12.6	0.748	0.241
Females	38.6 ± 15	41.1 ± 14	0.524	39.8 ± 14.4	36.8 ± 9.01	0.128	0.438
Weight, kg							
Males	67.9 ± 8.5	70.9 ± 11.1	0.204	69.7 ± 10.2	78.4 ± 12.7	0.000	0.000‡
Females	55.4 ± 9.25	60.8 ± 12.3	0.051	58.0 ± 11.1	60.9 ± 7.68	0.155	0.042§
BMI, kg/m[b]							
Males	23.1 ± 2.5	23.7 ± 3.6	0.363	23.5 ± 3.2	25.3 ± 3.78	0.005	0.014§
Females	21.9 ± 3.7	23.7 ± 4.7	0.989	22.7 ± 4.3	23.1 ± 2.7	0.682	0.149
FFM, kg							
Males	56.3 ± 6.6	55.8 ± 6.4	0.719	56.0 ± 6.5	61.9 ± 8.3	0.000	0.000‡
Females	39.5 ± 6.7	39.6 ± 4.9	0.919	39.6 ± 5.9	42.5 ± 5.3	0.014	0.051‡
FM kg							
Males	11.6 ± 6.2	15.1 ± 7.9	0.038	13.7 ± 7.4	16.5 ± 8.7	0.047	0.026§
Females	15.9 ± 6.6	21.2 ± 9.0	0.015	18.5 ± 8.2	18.4 ± 5.9	0.989	0.025§
FM, %							
Males	16.7 ± 7.8	20.4 ± 8.4	0.046	18.9 ± 8.4	20.3 ± 8.1	0.319	0.079
Females	28.2 ± 9.2	33.7 ± 7.8	0.019	30.9 ± 8.9	29.9 ± 6.6	0.600	0.030§
HGS, kg							
Males	35.7 ± 7.1	34.7 ± 7.4	0.552	35.1 ± 7.2	39.9 ± 4.4	0.000	0.001‡
Females	23.7 ± 6.0	23.2 ± 5.3	0.440	18.7 ± 4.6	26.7 ± 4.8	0.000	0.000‡
Total PhA, (°)							
Males	6.58 ± 0.92	6.95 ± 0.84	0.048	6.80 ± 0.89	6.88 ± 0.73	0.065	0.033§
Females	5.52 ± 0.54	5.93 ± 0.60	0.008	5.72 ± 0.60	6.28 ± 0.45	0.000	0.000‡
Arms PhA, (°)							
Males	5.23 ± 0.80	5.32 ± 0.82	0.643	5.29 ± 0.81	5.61 ± 0.86	0.037	0.104
Females	3.81 ± 0.69	4.07 ± 0.57	0.123	3.94 ± 0.64	4.77 ± 1.01	0.000	0.000‡
Legs PhA, (°)							
Males	7.47 ± 1.25	8.23 ± 1.09	0.005	7.93 ± 1.21	8.26 ± 1.17	0.148	0.006§
Females	6.86 ± 0.84	7.46 ± 0.76	0.007	7.16 ± 0.85	7.14 ± 1.29	0.959	0.049§

CDAI: Chron's Disease Activity Index; FFM: fat free mass; FM: fat mass; HGS: handgrip strength, PhA: phase angle.
[a] Un-paired T test between active vs. quiescent.
[b] Un-paired T test between all vs. controls.
[c] ANOVA test among active, quiescent and controls with significant values between:(§) active vs. controls; (‡) active and quiescent vs. control.

3.3. Biochemical markers

Both nutritional and inflammatory markers were assessed in all CD patients, as presented in Table 5. The data showed that Hb, albumin, prealbumin, total protein and pseudocholinesterase were lower in active CD patients than in the quiescent group (p < 0.05), while the alpha-2 fraction, fibrinogen and CRP were higher (p < 0.05). Additionally, those variables were correlated with total PhA, observing a direct association with Hb (r = 0.299; p = 0.000), albumin (r = 0.389; p = 0.000), pre-albumin (r = 0.195; p = 0.023) and total protein (r = 0.202;

p = 0.01). An inverse correlation with PhA was found for the alfa-2 fraction (r = −0.192; p = 0.022) and fibrinogen (r = −0.246; p = 0.003).

3.4. Disease duration, location and behavior

Among the 140 patients, 92 had a disease duration >5 years and 44 had a disease duration between 1 and 5 years, while 4 patients had a recent diagnosis (<1 year). Comparing the 2 largest groups, no difference was found in FFM or PhA values, even when the analysis was stratified by sex.

Table 4
Pearson's correlation coefficients between total phase angle, individual characteristics and BIA parameters.

	Active (n = 62)	Quiescent (n = 78)	All (n = 140)
Age, years	−0.254*	−0.453**	−0.362**
CDAI	−0.211	−0.123	0.135**
Weight, kg	0.356**	0.290**	0.353**
BMI, kg/m^2	0.138	0.087	0.146
FFM, kg	0.383**	0.486**	0.443**
FM kg	−0.057	−0.129	−0.035
FM, %	−0.196	−0.304**	−0.296*
HGS, kg	0.588**	0.514**	0.539**

CDAI: Chron's Disease Activity Index; FFM: fat free mass; FM: fat mass; HGS: handgrip strength.
*$p < 0.05$; **$p < 0.001$.

With regard to disease location (Montreal classification), we observed that the disease was mainly located in the ileum-colon (L3, n = 80), followed by the ileum (L1, n = 46). By analyzing patients according to disease location (L1 vs. L3), we did not find differences between patients, except for FFM, which was lower in males in the L3 group than in those in the L1 group (L1: FFM = 58.4 ± 5.5 kg vs. L3: FFM = 53.9 ± 6.6 kg; p = 0.003). Disease behavior did not influence any of the nutritional or functional variables considered.
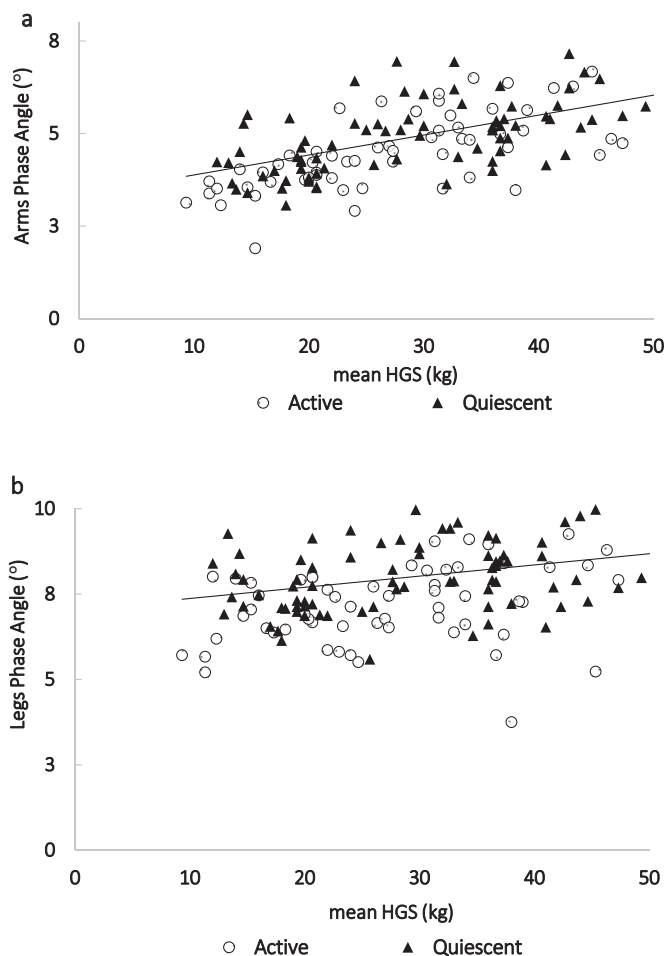

Fig. 1. Correlation between arms (a) and legs (b) PhA values with mean HGS. Linear correlation was applied for assessing the relation between both arms (a) and legs (b) PhA values with mean HGS in all CD patients, taking CDAI differences into account.

3.5. Treatment

Finally, CD patients were split into three groups according to therapies as follows: 1) biologic (infliximab n = 17, adalimumab n = 32, and vedolizumab n = 7), 2) conventional (immunosuppressives + mesalazine) and 3) no therapy. ANOVA post hoc analysis did not reveal any significant difference in PhA, BC or muscle strength between treatment groups (Table 6); however, both total- and segmental-PhA (arms and legs) were higher, albeit not significantly, in the biologic group. Indeed, compared to controls, total PhA was significantly lower in both the conventional and no therapy groups, but not for patients on biologic treatment. All CD groups showed lower arm-PhA and HGS values than the control group, while only patients not undergoing therapy had a lower body weight.

4. Discussion

This cross-sectional study aimed to investigate the nutritional status of patients with CD by assessing body composition, phase angle and muscle strength. Our findings showed that BIA-derived PhA is a valid indicator of nutritional status in CD patients and that its values decreased with increasing disease activity. The results showed that patients in the active phase had a lower FM than those who were clinically quiescent, while all of them, unrelated to CDAI and sex, had significantly lower lean mass and muscle strength than the age-, sex- and BMI-matched healthy controls. Finally, drug treatments did not influence any of the nutritional variables considered, although PhA was slightly better in patients receiving biologic therapy.

Patients with CD usually develop secondary malnutrition. The most widely used parameter to assess nutritional status is BMI, but taken alone, BMI is inaccurate. In fact, even with an apparently normal BMI, abnormalities in both FFM and FM distribution can be observed [31]. Overall, it has been recognized that altered BC among CD patients may negatively impact the course of the illness, response to therapies and surgery outcomes [4]. Thus, clinical awareness of BC evaluation and appropriate nutritional management may lead to improved outcomes for patients with this chronic disease.

The results of the BC evaluation presented by previous studies suggested that CD patients are affected by alterations in FM and FFM, which may not be detected or easily recognized by routine clinical assessment [4]. Generally, they tend to develop a relative reduction in lean mass and an increase in adiposity over time, but data are still contrasting due to differences in study design and characteristics of the included patients [32−34]. Based on BMI criteria, we found that only 9 out of 140 CD patients were underweight and therefore at increased risk of malnutrition. However, after performing BC analysis, we observed that all active CD patients had lower FM and body weight than the quiescent CD patients, but no difference was found in FFM, even when data were separated by sex. Similar results were reported by Yadav et al. [33], who showed a progressive, though not statistically significant, decline in BMI and FM (expressed as absolute and percentage values) with an increase in disease severity, but there was no effect on FFM. Still, the results from Back et al. [34] showed lower BMI and mid-arm circumference in active CD patients than quiescent patients.

Compared to controls, we found that FFM was significantly lower in both CDAI groups, while FM decreased in the active group only. In detail, our female patients had lower FFM values than controls, even though their BMI did not differ. Similar results were observed by Weich et al. [35] in adolescent CD patients and by Filippi et al. [36], who reported low FM in quiescent adult CD

Table 5
Biochemical parameters in all CD patients as well as according to disease activity.

	Active (n = 62)	Quiescent (n = 78)	All (n = 140)
	Mean ± SD	Mean ± SD	Mean ± SD
Hemoglobin, g/dl	12.8 ± 1.44**	13.9 ± 1.63	13.4 ± 1.63
Lymphocyte, 10^{-3}/ml	1.74 ± 0.66	1.61 ± 0.58	1.67 ± 0.62
Albumin, g/dl	3.90 ± 0.55**	4.29 ± 0.45	4.12 ± 0.53
Pre-albumin, g/L	0.23 ± 0.08*	0.33 ± 0.34	0.28 ± 0.26
Total protein, g/dl	6.66 ± 0.85**	7.13 ± 0.68	6.92 ± 0.79
Pseudo-cholinesterase, UI	8346 ± 2574*	9281 ± 2010	8868 ± 2796
alfa2 Fraction, %	11.3 ± 2.38**	10.0 ± 2.17	10.6 ± 2.35
Transferrin, g/L	2.48 ± 0.61	2.59 ± 0.49	2.54 ± 0.55
Total Cholesterol, mg/dl	148 ± 41.3	157 ± 44.2	153 ± 43
Fibrinogen, mg/dl	402 ± 92.0**	347 ± 84.9	372 ± 92.0
Ferritin (median, IQR), ng/ml	41 (74)	63 (82)	53.5 (80)
CRP (median, IQR), mg/l	5 (9.8) *	2.0 (6.1)	3.15 (8.0)

CRP: C-reactive protein, Interquartile Range (IQR); ***p < 0.05; **p < 0.001**.

Table 6
Age, BMI, body composition, handgrip strength and phase angle according to treatment.

	Biologics (n = 56)	Conventional (n = 40)	No therapy (n = 43)	Controls (n = 83)	p^a
Age, years	38.3 ± 13.6	40.0 ± 14.6	38.3 ± 14.1	37.5 ± 11.0	0.799
Weight, kg	65.0 ± 10.9	66.1 ± 13.9	64.1 ± 11.7	70.5 ± 13.9	0.016*
BMI, kg/m²	22.8 ± 3.25	23.7 ± 4.86	23.1 ± 3.02	24.2 ± 3.5	0.105
FFM, kg	49.5 ± 8.83	49.7 ± 10.3	48.2 ± 11.9	53 ± 12.1	0.085
FAT, kg	15.1 ± 7.26	16.4 ± 9.59	15.9 ± 7.75	17.5 ± 7.64	0.338
FAT, %	23.0 ± 9.39	24.1 ± 10.7	24.9 ± 11.4	24.8 ± 8.78	0.692
HGS, kg	28.9 ± 9.19	27.1 ± 10.2	28.3 ± 11.7	33.8 ± 7.97	0.000°
Total PhA, (°)	6.50 ± 0.89	6.23 ± 0.99	6.28 ± 0.87	6.81 ± 0.79	0.001^
Arms PhA, (°)	4.85 ± 1.00	4.62 ± 0.17	4.69 ± 0.91	5.30 ± 1.02	0.001°
Legs PhA, (°)	7.74 ± 1.34	7.57 ± 1.13	7.51 ± 1.28	7.75 ± 1.34	0.663

BMI: body mass index, FFM: fat free mass; FM: fat mass; HGS: handgrip strength, PhA: phase angle.
[a] ANOVA test showing with significant values between: (*) No therapy vs. controls; (°) All groups vs. controls and (^) Conventional and No therapy vs. controls.

patients, while Valentini et al. [37] did not find any differences in BC between healthy individuals and CD patients.

A variety of methods can be employed to measure BC, such as dual energy X-ray absorptiometry (DXA), dilution techniques, BIA, air-displacement plethysmography (ADP) or magnetic resonance imaging (MRI), but none of them are error free [38]. Generally, the more advanced techniques are less accessible, time-consuming and more costly and as a result are not always feasible in clinical practices. Moreover, some tools, such as the isotopes dilution technique, BIA or ADP, can result in lower accuracy if used in different clinical conditions because they require the assumption of a constant hydration state [38].

Nevertheless, from BIA, we can directly measure PhA, an index of soft tissue mass quality, which has gained great popularity in nutritional assessment and monitoring in recent years. Indeed, a higher PhA reflects higher cellularity, cell membrane integrity and cell function, whereas reduced PhA reflects lower integrity and quality cell mass and is associated with unfavorable disease progression and poor prognosis. Indeed, disease-related malnutrition as well as mortality rate [14] have been shown to be associated with altered electric properties of the tissues that are detectable by BIA [39].

Generally, PhA ranges between 5° and 7° in healthy subjects [40,41], and in athletes, it might reach 8.5° [42], but several factors, such as diseases, inflammation, infection, etc. could affect those values. In this study, the mean PhA value was within the normal range; however, we observed a small decline with the increase of disease activity in both sexes, resulting in levels lower than those in healthy subjects.

Back et al. [34] did not find any differences in PhA values between active and quiescent CD patients (p = 0.75), while Wiech et al. [35] showed that PhA was reduced in adolescent CD patients compared to the values of the controls. Interestingly, we found that PhA was inversely correlated with CDAI, age and FM, while it was positively associated with FFM and HGS, which was in accordance with previous results [5]. However, by controlling for age and sex, we found that PhA was still significantly correlated with body weight, BMI, FM, HGS and CDAI but not with FFM. Although PhA can reveal both changes in the amount and quality of soft tissue mass, it is not strictly associated with FFM values, especially in disease conditions. Indeed, BIA results are population-specific and mostly dependent on the prediction equation used to estimate FFM and FM. As previously reported in a healthy population, the main determinants of PhA values are sex and age [40,41]. Interestingly, by performing a multivariate linear regression analysis in this sample, we confirmed the predictive role of sex and age in PhA values and identified CDAI as an additional predictor. Precisely, regression coefficients were negative for age and CDAI, implying a decrease in PhA with aging as well as with stronger disease activity, while it was positive for sex, as previously shown [40,41].

To our knowledge, this is the first study to assess PhA in different body compartments, such as arms and legs. Segmental PhA data showed that leg-PhA significantly differed between the active and quiescent groups, resulting in higher sensitivity than that of arm-PhA in detecting changes between intra- and extracellular water. Similar results were also reported by a previous study performed by our group in cyclists, showing that leg-PhA was correlated strongly with changes in water distribution [43].

PhA is also associated with muscle functionality [44]. The handgrip strength measure is a simple tool that may be easily performed in the clinical setting and is known to correlate well with overall strength [45]. In our patients, we found that HGS was significantly lower than in controls, but there was no difference between the CDAI groups. Although the mean HGS observed in CD patients appeared to be normal, 41% of patients had HGS values below the cut-off points

(>30 kg for males and >20 kg for females) [46]. According to the literature, Lu et al. [47] observed that HGS was lower in both males and females with CD than in controls (p < 0.001); however, HGS was also significantly higher in male CD patients with inactive disease than in those with active disease (p < 0.05), as we found.

From a biochemical point of view, small differences in nutritional and inflammatory markers emerged between active and quiescent CD groups, contributing to the evaluation of nutritional status in these patients. As expected, active CD patients had higher levels of fibrinogen, CRP and alpha-2 fraction at the protein electrophoresis than the quiescent group, while albumin, prealbumin, total protein, pseudocholinesterase and HB concentrations were reduced. Previous studies [34,48] showed that HB was lower in active CD patients than in quiescent patients, whereas albumin, CRP and total protein did not differ. Interestingly, all serum protein markers, such as albumin, prealbumin and total protein, were directly correlated with PhA, while fibrinogen and CRP were inversely associated. Therefore, these data highlighted that low protein markers and high inflammatory status can impair PhA values.

Finally, we analyzed the possible effect of drugs, especially biologic therapy, on nutritional parameters since current data are still unclear. Emerenziani et al. [19] reported increased PhA values in 23 clinical remission patients on infliximab therapy compared to the values of those on conventional therapy. In addition, they also showed that in 12 active CD patients, following the induction protocol with infliximab, FFM increased, albeit not significantly, and PhA normalized. However, Santos et al. [20] showed that PhA did not improve after 24 weeks of infliximab therapy in 23 CD patients (p = 0.53), and some differences were observed in BC, with a substantial increase in FM compared to FFM. Our findings did not show any significant differences between CD patients, although both total and segmental PhA were slightly higher, albeit not significantly, in those on biologic therapy compared to the values of patients on conventional therapy or no therapy. It should be specified, however, that among patients on biologic therapy, approximately 40% started therapy less than 3 months prior; nevertheless, no differences were observed when they were removed from the analysis.

Our study had some limitations. Although BIA is a valid and reliable tool for BC analysis in clinical practice, it can be influenced by the state of hydration, which can often result in modifications in the results of CD patients due to diarrhea and malabsorption. Nevertheless, PhA, which does not strictly require algorithm-inherent errors or assumptions such as constant tissue hydration [5], could be useful for screening and monitoring the nutritional status of these patients. Additionally, the study design adopted (cross-sectional) and the lack of physical activity data can be considered further limitations.

In conclusion, PhA is a valid tool to assess nutritional status in CD patients, as supported by nutritional biomarker evaluation, and its values decreased with increasing disease activity. Although we included CD patients with mild to moderate disease activity, we observed reduced muscle strength in patients of both sexes compared to that of controls, and small alterations in BC can be considered a marker of nutritional deficiency. Therefore, the assessment of BC, specifically of BIA-derived PhA, should be recommended in clinical practice for screening and monitoring the nutritional status of CD patients.

Conflict of interest

Authors declare no conflict of interest.

Statement and funding sources

State of authorship

I.C., F.Co., and F.P. conceptualized and designed the study, N.I., M.C.P., R.S., L.A., A.T., F.Ca. and L.S. collected the data, M.M. and I.C. analyzed and interpreted the data, I.C. wrote the manuscript and all authors participated to the discussion of results and critically commented the manuscript for the final approval.

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