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Original article

Impaired nutritional status in outpatients in remission or with active Crohn's disease – classified by objective endoscopic and imaging assessments

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SUMMARY

Background and aims: Crohn's disease is a chronic inflammatory disease consisting of alternated periods of relapse and remission. The disease is associated with altered body composition and micronutrient deficiencies. This study aimed to evaluate the nutritional status of Crohn's disease outpatients in remission and activity of the disease.

Methods: Patients were classified according to Crohn's Disease Endoscopic Index of Severity or Magnetic Resonance Imaging scan. Anthropometric and biochemical analysis was performed for nutritional status evaluation.

Results: A total of 60 patients were evaluated of which 31 were in endoscopic remission (mean Crohn's Disease Endoscopic Index of Severity: 1.76) and 29 in activity (mean Crohn's Disease Endoscopic Index of Severity: 7.88). Regarding markers of fat and lean mass, lower values were observed in the activity group when compared to the remission group ($p < 0.05$). There was a positive correlation regarding the duration of the disease and the anthropometric parameters in patients with active disease. Interestingly, the prevalence of overweight/obese patients was 55% in remission group and 28% in activity group according to the Body Mass Index classification. In addition, lower levels of iron, folic acid and albumin were also observed in Crohn's disease activity group.

Conclusions: We observed important differences in nutritional markers between patients in remission and activity phases, with higher prevalence of overweight/obese in patients with remission of the disease.

1. Introduction

Crohn's disease (CD) is an inflammatory bowel disease, characterized by a chronic transmural inflammation presenting areas affected by granuloma, hyperemia, lymphoid hyperplasia and fibrosis, and any part of the digestive tract may be affected [1]. CD symptoms consists of abdominal pain, diarrhea, malaise, anorexia, fever and weight loss [2]. Patients have intermittent crises, with alternating periods of relapse (active disease) and remission and identifying the correct phase is crucial for adjust therapy [3,4]. These phases can be characterized by endoscopic scores or magnetic resonance imaging (MRI) scan, which are objective tools for evaluating the degree of CD activity, and the Crohn's Disease Endoscopic Index of Severity (CDEIS) is one of the endoscopic scoring systems [5,6].

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The nutritional status of these patients is usually altered. Malnutrition is reported in 20%–80% [7–9] and there are several factors involved in this condition, such as low dietary intake, increased intestinal loss, metabolic disorders, increase in nutritional requirements, drug's interaction and nutrients malabsorption [10]. Impairment of nutritional status appears to be related to location, activity and duration of the disease [11]. In addition, CD is associated with micronutrient deficiencies, which are the most frequent nutritional abnormalities in the remission state [12].

Although malnutrition is common in CD, mainly in the active phase, there are many patients in a good nutritional status and even overweight [13]. Previous studies have shown an increased prevalence of overweight and obesity [14,15]. Obesity in CD patients has been associated with a more severe clinical course, elevated inflammatory markers [16], anorectal complications, increase in hospitalization and obese patients are more likely to require steroids [17]. CD is also associated with changes in mesenteric adipose tissue, including increased adiposity near the intestinal affected area, besides abnormalities in the histological analysis, such as infiltration of macrophages and fibrosis [18,19]. Adipose tissue is able to release adipokines which can lead to pro- or anti-inflammatory pathways, suggesting that this tissue may represent a relevant role in the pathogenesis of CD [20,21].

The results of the assessment of body composition in adult CD patients have been heterogeneous and there are no studies so far assessing the nutritional status in both stages of the disease classified according to the endoscopic and radiological activity. Therefore, the aim of this study was to assess the nutritional status of outpatients with CD in remission and activity stages.

2. Methods

2.1. Study subjects

Adult subjects were recruited in this cross-sectional study from the IBD outpatient clinic of the Coloproctology Unit at the Gastrocenter of the University of Campinas (UNICAMP) from May 2017 through July 2018. The diagnosis of CD was based on endoscopic, radiological, and histological criteria. Inclusion criteria were: age between 18 and 60 years, with ileal and/or colonic location of the disease. Exclusion criteria were: pregnant and breastfeeding women, patients with edema and patients who did not have endoscopic or imaging tests. All patients were interviewed and demographic and clinical data were collected.

This study protocol was approved by the Ethics Committee of the University of Campinas (CAAE n 62802016.0.0000.5404) and a written consent form was obtained from all patients before the study.

2.2. Endoscopic and imaging assessment

Disease activity was assessed by colonoscopy examination (defined as CDEIS $\geq$ 5 or the presence of deep ulcers in at least one intestinal segment) [5] or by nuclear magnetic resonance scan enterography (defined as the presence of deep ulcers in at least one intestinal segment, besides edema and creeping mesenteric fat near the affected intestinal area). According to these criteria, patients were divided in two groups, activity and remission. The Montreal classification was used to classify the patients according to the age of diagnosis, location and behavior disease [22,23].

2.3. Anthropometric parameters

Nutritional status was determined using the anthropometric parameters. Weight and height were measured and the body mass index (BMI) was calculated. Calf circumference (CC) and mid-arm circumference (MAC) were measured using a measuring tape and the triceps skinfold thickness (TSF) was obtained using skinfold caliper (Lange Caliper – Cambridge Scientific, USA). Circumferences and skinfold were measured three times and the mean values were used. Mid-arm muscle circumference (MAMC), mid-arm muscle area (MAMA) and weight loss (past 3 months) were calculated.

BMI (kg/m^2) were classified according to World Health Organization following the cut-off points for low weight <18.5, eutrophic 18.5–24.9, overweight 25–29.9 and obesity >30 [24]. The results of the CC, MAC, TSF, MAMC, MAMA and weight loss were compared according to reference values [25–27].

2.4. Biochemical tests

The following biochemical parameters were compared with reference values: iron (male: 70–180 ug/dL, female: 60–180 ug/dL), ferritin (male: 30–400 ng/mL, female: 13–150 ng/mL), folic acid (3.9–26.8 ng/mL), vitamin B12 (197–771 pg/mL), albumin (3.5–5.2 g/dL), prealbumin (20–40 mg/dL), transferrin (255–450 ug/dL), zinc (80–120 mcg/dL), magnesium (male: 1.5–2.1 mEq/L, female: 1.6–2.1 mEq/L), total cholesterol (<190 mg/dL), C-reactive protein (CRP) ($\leq$3 mg/L), erythrocyte sedimentation rate (ESR) (male: up to 10 mm-1h, female: up to 14 mm-1h), hemoglobin (Hb) (male: 14–18 g/dL, female: 12–16 g/dL) and hematocrit (Ht) (male: 41–52%, female: 36–46%).

2.5. Statistical analysis

Results are expressed as means and standard deviations (SD), and percentage. Categorical variables were compared with the Chi-square (χ^2) test. Continuous variables with normal distribution were analyzed by Student's *t* test, and *Mann–Whitney* test was used for the non-parametric variables. STATA 12.0 software was used for statistical analyses. The *p* value of <0.05 was considered statistically significant.

3. Results

The demographic and clinical characteristics of the 60 patients we evaluated are listed in Table 1. The mean of CDEIS in activity group was 7.88, significantly higher in comparison to the remission group, 1.76 ($p < 0.001$). The mean of CDAI in remission and activity patients were 41.35 and 88.2, respectively, corresponding both to clinical remission. Among the remission patients, 55.17% were women and 51.61% of activity patients were men. There were no differences in the variables gender, smoking, Montreal classification and previous surgeries between the two groups. The mean duration of the disease in remission patients was higher than activity patients (12.64 vs 8.27 years, respectively) and patients with active disease were younger than patients in remission ($p = 0.027$).

When anthropometric parameters were compared between groups (Table 2), there was a significant difference in BMI ($p = 0.022$). Since BMI alone does not reflect the proportion of muscle and fat mass, we evaluated markers of fat and lean mass. We observed differences in CC ($p = 0.034$), MAC ($p = 0.005$), TSF ($p = 0.020$), MAMC ($p = 0.022$) and weight loss ($p = 0.007$) in activity compared with remission patients. This analysis showed that patients with active disease had impaired nutritional status when compared to patients in remission.

Significant or severe weight loss from the past 3 months ($\geq$7.5%) was not observed in both groups, but patients with active CD showed higher weight loss than those in remission ($p = 0.007$). According to WHO classification to BMI, no remission patients presented low body weight while 20.69% of activity patients were

Table 1
Demographic and clinical characteristics of patients.

Variables	Remission (n = 31)	Activity (n = 29)	*p* value
Gender (M/F) (%)	48.39/55.17	51.61/44.83	0.599
Age (years)	39.67 (±10.43)	33.82 (±8.58)	0.027
Smoking (%)	3.23	0	0.329
Duration of the disease (years)	12.64 (±7.25)	8.27 (±7)	0.021
[a]Age at diagnosis (%)			
A1	3.23	6.9	0.514
A2	74.19	86.21	0.245
A3	22.58	6.9	0.089
[a]Disease location (%)			
L1	25.81	27.59	0.876
L2	29.03	17.24	0.281
L3	45.16	55.17	0.438
L4	0	0	–
[a]Disease behavior (%)			
B1	48.39	55.17	0.599
B2	41.94	31.03	0.381
B3	9.68	13.79	0.620
Perianal disease (%)	62.96	37.04	0.113
Previous surgeries (%)	56.82	43.18	0.185
Inflammation in MRI (yes/no)	0/10	16/0	<0.001
CDAI	41.35 (±41.2)	88.2 (±54.67)	0.001
CDEIS	1.76 (±0.38)	7.88 (±1.82)	<0.001

[a] Montreal Classification: A1: below 16 years; A2: between 17 and 40 years; A3: above 40 years; L1: ileal; L2: colonic; L3: ileocolonic; L4: isolated upper disease; B1: non-stricturing, non-penetrating; B2: stricturing; B3: penetrating; MRI: Magnetic Resonance Imaging; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity.

Table 2
Anthropometric analysis of patients.

Variables	Remission (n = 31)	Activity (n = 29)	*p* value
BMI (kg/m^2)	25.67 (±4.89)	22.60 (±3.81)	0.022
Low weight (%)	0	20.69	
Eutrophic (%)	45.16	51.72	
Overweight (%)	38.71	24.14	
Obesity (%)	16.13	3.45	
CC (cm)	38 (±3.66)	35.96 (±3.49)	0.034
MAC (cm)	31.69 (±4.38)	28.46 (±4.19)	0.005
TSF (mm)	18.53 (±6.32)	14.24 (±7.55)	0.020
MAMC (cm)	26.30 (±4.33)	23.99 (±3.19)	0.022
MAMA (cm^2)	56.51 (±18.68)	46.60 (±12.18)	0.066
Weight loss (%)	1.35 (±3.10)	4.43 (±5.40)	0.007

BMI: body mass index; CC: Calf circumference; MAC: mid-arm circumference; TSF: triceps skinfold thickness; MAMC: mid-arm muscle circumference; MAMA: mid-arm muscle area.
Student's t test performed for parametric variables: MAC, TSF, MAMC.
Mann–Whitney test performed for non-parametric variables: BMI, CC, MAMA, weight loss.

classified as malnourished. We observed a high percentage of overweight of 38.71% and 24.14% in remission and activity groups, respectively. In addition, obesity was documented in 16.13% in remission and 3.45% in active CD.

Having observed important differences in nutritional status and duration of the disease, we performed the correlation test with these variables. As shown in Table 3 there were positive correlations between anthropometric parameters and duration of the disease in activity group. Among the parameters, BMI (r = 0.402, $p = 0.030$), CC (r = 0.386, $p = 0.038$), MAC (r = 0.495, $p = 0.006$), MAMC (r = 0.555, $p = 0.001$), and MAMA (r = 0.575, $p = 0.001$) showed a significant correlation, suggesting that the shorter the duration of the disease, the lower the values for anthropometric parameters were observed. No correlations were observed for TSF and weight loss for activity group and no correlations were observed in remission group.

Table 3
Correlation between anthropometric parameters and duration of the disease.

Variables	r (remission)	*p* value	r (activity)	*p* value
BMI	−0.095	0.611	0.402	0.030
CC	−0.019	0.917	0.386	0.038
MAC	−0.062	0.737	0.495	0.006
TSF	−0.146	0.432	0.127	0.510
MAMC	0.092	0.619	0.555	0.001
MAMA	0.122	0.511	0.575	0.001
Weight loss	−0.058	0.755	−0.198	0.301

BMI: body mass index; CC: Calf circumference; MAC: mid-arm circumference; TSF: triceps skinfold thickness; MAMC: mid-arm muscle circumference; MAMA: mid-arm muscle area. r = Pearson correlation coefficient.

Regarding biochemical parameters, iron ($p = 0.020$), folic acid ($p = 0.012$), albumin ($p = 0.002$) and total cholesterol ($p = 0.030$) were decreased in patients with active disease (Table 4). It is important to highlight the percentage of inadequacy for iron (66.67%), zinc (60%), CRP (64.29%) and ESR (88%) in active group and also for zinc (45%) and ESR (76.92%) in remission patients.

4. Discussion

The use of objective assessment by indices that are representative of patients in remission or activity, such as Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's disease (SES-CD) is generally recognized as being important [5,28]. The endoscopic scoring system allows standardization, reduces inter-observer variability and can be used as an indicator of disease course [29]. Similarly, another objective method may be used: imaging assessment, which is a non-invasive technique that allows evaluation of small bowel segments, detection of disease complications and assessment of disease activity [30,31]. In contrast, the clinical index Crohn's Disease Activity Index (CDAI) is a subjective method for assessing the presence and severity of intestinal inflammation, has a high variability [6,32]. In spite of its widespread use to classify disease activity, it does not provide a good correlation with the endoscopy evaluation.

Accordingly, our results have shown that endoscopic index had more sensitivity than clinic index to detect inflammation in CD patients, as indicated by 89.28% percent of patients who were not classified as active using the clinical method in activity group. To

Table 4
Biochemical analysis of nutritional and inflammatory indices.

Variables	Remission (n = 31)	Activity (n = 29)	*p* value
Iron	85.76 (±37.76)	64.02 (±49.58)	0.020
<reference, %	30.77	66.67	
Ferritin	152.73 (±253.49)	86.3 (±92.89)	0.288
<reference, %	12.5	26.92	
Folic acid	12.7 (±4.09)	9.82 (±3.8)	0.012
<3.9 ng/mL, %	0	3.7	
Vitamin B12	415.26 (±210.95)	406.74 (±255.41)	0.727
<197 pg/mL, %	4.17	25.93	
Albumin	4.23 (±0.38)	3.79 (±0.60)	0.002
<3.5 g/dL, %	3.7	24.14	
Prealbumin	30.37 (±11.44)	26.7 (±10.77)	0.258
<20 mg/dL, %	17.39	16	
Transferrin	332.14 (±98.94)	319.29 (±79.25)	0.616
<255 ug/dL, %	17.39	15.38	
Zinc	82.1 (±18.95)	76.33 (±17.19)	0.291
<80 mcg/dL, %	45	60	
Magnesium	1.74 (±0.23)	1.76 (±0.24)	0.992
<reference, %	15.38	16	
Total cholesterol	170.08 (±38.28)	146.52 (±38.15)	0.030
>190 mg/dL, %	30.77	15.38	
Hb	13.82 (±1.61)	12.99 (±2.22)	0.103
<reference, %	17.24	27.59	
Ht	41.38 (±4.34)	39.37 (±5.93)	0.139
<reference, %	12.9	31.03	
CRP	2.28 (±1.88)	18.66 (±30.2)	0.001
≥3 mg/L, %	29.63	64.29	
ESR	24.8 (±18.35)	38.04 (±32.29)	0.313
<reference, %	76.92	88	

Hb: hemoglobin; Ht: hematocrit; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.
Student's t test performed for parametric variables: folic acid, prealbumin, transferrin, zinc, total cholesterol, hb, ht.
Mann–Whitney test performed for non-parametric variables: iron, ferritin, vitamin B12, albumin, magnesium, CRP, ESR.

our knowledge, this is the first study to use objective tools as endoscopic and imaging evaluation to classify activity in CD patients for nutritional assessment.

We assessed the nutritional status using anthropometric and biochemical parameters, since it is widely available, suitable, accurate and comparable to other methods. As reported earlier, 22.6% of our patients in activity were classified as malnourished and presented significant differences in relation to lean and fat mass. Benjamin et al. compared 77 patients in remission CD with 35 in active disease and reported similar results regarding lean and fat mass [33]. Rocha et al. demonstrated that fat mass depletion was associated with active phase of CD patients [10]. Mijač et al. found that malnutrition was common in patients with active CD assessed by anthropometric measurements, confirming that malnutrition is a substantial problem among CD patients [9]. Loss of lean mass may be associated with morbidity, loss of muscle function, fatigue and decreased strength, altered energy metabolism and increased susceptibility to infections [34,35]. The elevated muscle active cytokines in CD, such as TNF-α, interleukin 1β and interleukin 6 may stimulate protein degradation, inhibit myogenic differentiation and induce myoblast apoptosis, leading to deficits of lean mass [36]. Thereby, identifying malnourished patients is important to provide appropriate and immediate nutritional intervention [37].

The results of this study demonstrate that malnutrition is not the main nutritional feature of our patients since we also showed a high prevalence of overweight and obesity (55%) and cholesterol levels (31%) mainly in remission group. Our data corroborate other studies that reflect an important and modern era of changes in body composition in CD, associated with the use of more efficient drugs to improve the quality of life. Besides, during the last decades, most developing countries underwent a nutritional transition (or it is still in course), with changes in food intake (higher consumption of fats and simple carbohydrates, sugar, beverages, etc) and also with lower physical activity levels. It is plausible to say that CD patients may also have altered their life habits in recent years, and the growth of obesity that is observed in society as a whole is also observed among these patients, especially those in remission, with a lower incidence of symptoms.

The prevalence of overweight and obesity is associated with multiple chronic diseases, such as type 2 diabetes, hypertension, hypercholesterolemia, coronary heart disease and cancer [38], and it has been also reported as a growing problem in CD, leading to an increased risk especially for diseases of cardiovascular origin [35,37,39–41]. Nascimento et al. suggested that obesity in CD might be associated with a poor clinical outcome and presence of abscesses [42]. Similarly, Blain et al. demonstrated that overweight and obese patients had more frequent anoperineal complications and were more susceptible to active disease and to require hospitalization [17]. Ungar et al. evaluated severe/morbidly obese patients and found that these patients are more often affected by colonic disease [43]. In a retrospective cohort study it was reported that overweight CD patients were older at diagnosis and they had a significantly shorter time to first surgery than those with underweight [16].

Moreover, obesity could contribute to risk of CD, as numerous mechanisms have been described, such as alterations in the gut microbiome, epigenetic changes reported in both obesity and IBD patients and elevated levels of bowel inflammation [44–46]. The potential long-term implications of overweight and obese patients for inflammatory load in CD merit further study. Thus, these studies emphasize the need for nutritional follow-up of patients with active and remission CD phases.

We observed that the mean age of patients in activity was lower than those in remission, and the patients in activity showed positive correlations with impairment nutritional status, indicating an impact of the duration of the disease on nutritional status. Underweight condition begins many years before the disease so it may be a pre-clinical manifestation of the disease, and malnourished patients tend to be diagnosed at younger ages differently from obese patients in which the diagnosis occurs at a more advanced ages [47]. By contrast, Yadav et al. divided the patients into three categories of disease duration and observed decline in nutritional status with increased duration of the disease. However, since only nine patients had disease duration of <1 year, maybe the correlation could not be detected [48].

According to biochemical assessment, lower iron, folic acid and albumin levels were observed in activity when compared to remission group. Interestingly, 67% of patients in activity had subnormal serum levels of iron even without differences in ferritin and hemoglobin. This observation agrees with Vagianos et al. who reported that 39% of their patients had iron deficiency. Iron deficiency has been reported in many studies [45,47,49–51]. Azzopardi et al. evaluated 171 adult patients with CD and reported iron deficiency in 78% of those in activity and in 21% of patients in remission, and this deficiency was associated with some factors, like stricturing disease, use of TNF-α inhibitors and surgery [52]. Blood loss is considered one of the leading causes of iron deficiency, other causes are inadequate dietary intake and impaired iron absorption and utilization [53,54].

Albumin and prealbumin are negative acute-phase proteins and as such it could indicate active CD. The hypoalbuminemia is not necessarily related to undernutrition, however, since inflammation is a risk factor for malnutrition development, albumin may be considered as a useful predictor of complications and mortality [55,56]. Hypoalbuminemia was observed in 24% of our patients in activity and these findings are consistent with several previous

studies [33,52–54,57]. Higher CRP serum levels in activity compared to remission patients and elevated levels in both groups were found. CRP is an acute-phase inflammatory protein and a good predictor of remission and response to treatment, elevated CRP along with other parameters may be associated with a poor prognosis and loss of therapeutic response in CD [59].

In addition to not being different between the groups, remission and activity patients had a zinc deficiency of 45% and 60%, respectively. Zinc deficiency is also common in active and remission CD patients with a prevalence ranging from 15% to 40% and it has been associated with poor clinical outcomes, such as increase in hospitalizations, surgeries and disease complications [53,60,61].

Importantly, the results of the isolated biochemical parameters did not demonstrate the same impaired nutritional status as anthropometric methods in patients with active disease when compared to patients in remission. This suggests that both nutritional assessment methods should be included in all CD patients as part of the clinical routine.

In summary, patients in active CD have impairment of nutritional status and it had a positive correlation with the duration of the disease. In addition, patients with active disease were classified as malnourished and, surprisingly, a large proportion of patients in remission were overweight or obese. Objective methods such as endoscopic examination and MRI enterograghy are more accurate to classify CD activity compared to clinical methods. This leads to a better nutritional characterization and knowledge about the nutritional status of CD patients, which are limited in the literature.

Interpretation of our results should take some limitations into account. The cross-sectional design of study does not allow us to determine cause and effect factors. However, there are several strengths in the study. First, studies with CD patients in middle income countries are rare, and as nutritional transition is still in course for most of them, it is interesting to describe the differences in nutritional status according to the disease phase to better plan nutritional care. Besides, we showed several other markers of nutritional status that should be observed during patients' follow-up, like anthropometric and biochemical markers. In addition, future studies should be conducted to evaluate the impact of existing dietary risk factors and dietary patterns on nutritional status in both remission and active CD patients, and also longitudinal studies that could allow the follow up of the nutritional status according to the progression of the disease.

5. Conclusion

Our results show that CD patients in remission and activity phases have important differences in most of nutritional markers (anthropometric and biochemical), and also showed a large proportion of overweight and obesity in both groups, suggesting that nutritional assessment should be included in all CD patients as part of the clinical routine, since the extremes of nutritional status have been reported and it may have negative effects on the course of the disease.

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Statement of authorship

Each author's contribution is as follows:

Marina Moreira de Castro: intellectual planning, literature review, patient recruitment, data collection, analysis and writing of the manuscript.

Ligiana Pires Corona: intellectual planning, literature review, analysis and writing of the manuscript.

Lívia Bitencourt Pascoal: literature review, analysis and writing of the manuscript.

Bruno Lima Rodrigues: analysis and writing of the manuscript.

Maria de Lourdes Setsuko Ayrizono: intellectual planning and patient recruitment.

Claudio Saddy Rodrigues Coy: intellectual planning and patient recruitment.

Raquel Franco Leal: intellectual planning, literature review, patient recruitment and writing of the manuscript.

Marciane Milanski: intellectual planning, literature review, analysis and writing of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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