

Original Article

Nutritional Global Status and Its Impact in Crohn's Disease

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Abstract

Background: Malnutrition among inflammatory bowel disease (IBD) subjects is well documented in literature and may emerge from factors including inadequate dietary intake, malabsorption and disease activity. The aim of this study was to complete a comprehensive nutrition assessment and explore what possibilities may help bring a better quality of life for IBD subjects.

Methods: Nutritional status based on biochemical tests, body composition and body mass index (BMI). Food intake was assessed by an alternate 3-day food record and the adequacy of intake was evaluated according to national and international references. Clinical disease activity was evaluated by the Harvey-Bradshaw index and CRP levels.

Results: The study included 217 patients and 65 controls, where 54.4% of these patients were classified as normal weight with a mean BMI lower than controls (23.8 ± 4.9 versus 26.9 ± 4.8 kg/m², $P = 0.02$). Patients with disease activity showed more overweight and obesity than patients with controlled disease. Vitamin B12 deficiency was present in 19% of Crohn's disease (CD), mainly in patients with ileal commitment and small bowel resections. Anemia was present in 21.7% of patients, being more common in patients with active disease (25%) and bowel resection (23%). Regarding calorie intake (EI), CD group ingested more than controls (1986.3 ± 595.9 kcal versus 1701.8 ± 478.9 kcal; $P = 0.003$).

Conclusions: CD patients presented micronutrient deficiency when compared with controls, explained for other reasons than intake restrictions. Also, fat excess might have contributed to disease burden as continuously reported in the literature.

Keywords: *Crohn's disease; Diet; Dietary intake; Disease activity; Nutritional status*

Introduction

A number of nutritional disorders can be present in patients with Crohn's disease (CD) such as anorexia, malabsorption, protein-losing enteropathy or increased energy demand due to

hypermetabolism which might result in weight loss, malnutrition and nutritional deficiencies (1,2). Nevertheless, the literature suggests that poor food intake is one of the most important factors associated with the compromised nutritional status in

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CD (3). The risk increases when patients associate their food intake to what they believe to be causing their abdominal pain and diarrhea, or makes inadequate choices to decrease the symptoms. However, by doing that, they promote indiscriminately a poor distribution of macronutrient intake and dietetic insufficiency (2). Micronutrient deficiencies are commonly associated with this process and are aggravated by increased losses through the inflamed bowel. These deficiencies compromise the immune response, increase morbidity and impair the clinical response of therapeutic profiles (2,4).

Although insufficient food intake is a causal factor for nutritional deficits accepted in the literature, it is based on studies of specific CD subpopulations and may not represent outpatients with CD in general. A well-documented and analyzed diet pattern of a CD patient may help avoid unnecessary restrictions and improve their nutritional status.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional study was performed in individuals with diagnosed CD and healthy controls, comparing nutritional status and laboratorial parameters.

A total of 282 CD outpatients between the ages of 18 and 75 years old were consecutively selected; 217 CD patients (127 females and 90 males, ages between 18 and 73 years old) and 65 controls (40 females and 25 males, aged 20 and 61 years old) working at the same institution were included, although only 37 from the control group filled out a food intake questionnaire. All patients had a confirmed CD diagnosis and were enrolled at the *Grupo de Intestino do Ambulatório do Serviço de Gastroenterologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*. Clinical disease activity was evaluated by the Harvey-Bradshaw index and CRP levels. STROBE Statement Guidelines was adopted.

Exclusion criteria were diseases affecting their nutritional status like neoplasia or infective disease. Also, patients adapted to alternative diets (such as macrobiotic, vegetarianism, etc.) or pregnancy.

The Ethics Committee of the School of Medicine of the University of São Paulo *Hospital das Clínicas* approved the study. A written informed consent was obtained from each subject.

Dietary Assessment and Counseling

Nutritional status was assessed using anthropometric parameters: weight and body composition analysis were assessed by using a tetrapolar bioimpedance after overnight fasting. The height was measured using a wall mounted stadiometer. Body mass index (BMI) (5) is defined as the body mass divided by the square of the body height (kg/m^2) and

categorized as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI > 30 or greater). Albumin levels measures were observed for malnutrition, considering low and moderate depletion when 2.8–3.4 and 2.1–2.7 g/dL, respectively.

The nutritional status was evaluated by BMI, food intake by 3-day dietary recall to estimate the usual dietary intake, and nutritional composition (macro and micronutrients) using a software (DIET PRO v.5i) based on the Brazilian food composition database TACO (6) and enhanced data from the National Nutrient Database for Standard Reference (USDA) (7) Pinheiro et al. (8) and Fisberg and Villar (9) were references for the standardization of home cooking measurements and recipes.

In order to remove the within-person variability effect in food intake, the online program Multiple Source Method (10) was used. In order to remove the influence of the energy intake of nutrients for associations between nutrients and outcomes, the energy adjustment method proposed by Willett et al. (11) called nutrient residual, was performed.

Recommendations from the World Health Organization (WHO) (12) were used to assess the adequacy of macronutrient and cholesterol intake; for fiber intake, recommendations from the Food Guide for the Brazilian population (13) energy intake (EI) (12) the estimated energy requirement (EER), micronutrients (14) and the American energy average requirement (15).

Fasting blood samples were collected to determine the biochemical parameters of nutritional status: 25-hydroxide-vitamin D by a chemo-immunoassay, vitamin B12 and folic acid by electrochemiluminescence; zinc by atomic absorption spectrophotometry; magnesium and iron by colorimetric method; ferritin and C-reactive protein (CRP) by immunoturbidimetry. Complete blood count was performed by routine automated methods currently used at the hospital. Clinical activity was evaluated by Harvey Bradshaw Score (16).

Statistical Analysis

Statistical analysis was performed at SAS Studio on Demand for Academics Web page. Data distribution was analyzed using Normal-QQ-Plots, histogram Plots and Shapiro test. Numerical data was presented as median plus interquartile ranges [IQR]. Categorical data were summarized as the total percentage group and analyzed using Fisher's exact test (two-sided). Kruskal-Wallis Test was used to explore nonparametric data between two unpaired groups. The significance level adopted was 5%.

RESULTS

From January 2012 to December 2012, a total of 217 CD patients and 65 controls were screened. No differences found

in median age (36.6 versus 43.0, $P = 0.054$), proportion of patients over 65 years old (5.4 versus 7.8, $P = 1.0$) or female proportion (59% versus 58%, $P = 1.0$) between CD patients and control group.

Anthropometry and Diet Pattern

Out of the 217 CD enrolled in the study, 50.7% of patients were found presenting ileocolonic disease, followed by 36.3% in terminal ileum, colonic in 11.2% and 1.8% in superior digestive tract only. Stricturing disease was observed in 30.7%, followed by fistulizing in 27.4% and inflammatory in 25.9%. Previous abdominal surgery was observed in 83 (38.2%) patients. The total majority of 148 (68.2%) patients were in clinical remission through Harvey-Bradshaw index. The medical therapies used at time of the study were immunosuppressors 150 (69.1%), 5-ASA 115 (52.9%), Infliximabe 42 (19.4%) and Steroids 25 (16.1%) (Table 1).

CD patients showed more underweight and overweight than the control group ($P < 0.001$) and lean body mass was higher in the CD group ($P = 0.001$; Table 2). The depletion of albumin levels in the CD group was 4.8%, but there were no statistical differences when compared with the control group ($P = 0.375$; Table 2). Regarding calorie intake (EI), CD group ingested more than controls (1986.3 ± 595.9 kcal versus 1701.8 ± 478.9 kcal ($P = 0.003$). EER adequacy (<0.9 of ratio EI/EER) was

higher in the control group (89.2 versus 54.4%) as evidence that food ingestion was not the cause of depletion in CD patients from both EI and EER indicator.

Macronutrient and intake patterns showed a higher consumption of carbohydrates (245 g versus 214 g, $P = 0.004$) and fat (65.3 g versus 54.9 g, $P = 0.01$) in CD group and while protein intake remained similar (82.8 g versus 74.4 g, $P = 0.11$) when compared with controls. The food group analysis data showed CD patients consumed greater portions of vegetable oil (3.25 versus 2.18, $P < 0.0001$), salt (5.86 versus 3.68, $P = 0.0025$), cereals (5.03 versus 3.44, $P < 0.0001$), equal amounts of vegetables (3.47 versus 3.16, $P = 0.18$), fruits (1.18 versus 1.20, $P = 0.5$), dairy products (1.25 versus 1.05, $P = 0.25$), meat (1.7 versus 1.6, $P = 0.1$) and sugar (1.53 versus 1.51, $P = 0.15$). The dietary pattern analysis showed higher consumption of omega 6 in CD group (6.8 versus 5.6% kcal ($P < 0.001$). Fiber consumption remained similar between groups (21.2 g versus 20.7 g, $P = 0.78$). A high prevalence of micronutrients inadequacy intake was also observed, in CD patients and controls, mainly in regards to vitamins D (100%), E (100% and 96%, respectively), calcium (88% and 89%, respectively) and vitamin B6 (90% and 75%, respectively).

Micronutrient, Albumin and Lipids Serum Levels Profile

Biochemical analysis showed CD patients' increased deficiency of folic acid (10.6% versus 0%, $P = 0.03$), magnesium (18.4% versus 0%, $P = 0.002$), higher incidence of hypoalbuminemia

Table 1. Demographic characteristics of patients ($n = 217$)

Sex (male)	90 (41.5)
Age at diagnosis	
≤ 16 years	13 (6)
17–40 years	138 (63.6)
≥ 40 years	66 (30.4)
Disease location	
L1 (Ileal)	78 (36.3)
L2 (Colonic)	25 (11.6)
L3 (Ileocolonic)	112 (52.1)
L4 (Upper gastrointestinal)	4 (1.8)
Behaviour	
B1 (Inflammatory)	55 (25.9)
B2 (Stricturing)	65 (30.7)
B3 (Penetrating)	93 (27.4)
P (Perianal)	34 (16)
Intestinal resections	85 (39.2)
Disease activity	
Remission	148 (68.2)
Active disease	63 (29)
Medical therapy	
Imunosuppressor	150 (69.1)
Infliximabe	42 (19.4)
5-ASA	115 (52.9)
Steroids	35 (16.1)

Table 2. Nutritional profile of the patients (Crohn's disease patients $n = 217$; Controls $n = 65$)

	Crohn's disease	Controls	P value
Weight (kg) (mean \pm SD)	64.1 \pm 14.4	73.2 \pm 14.6	0.001
Height (m)	1.64 \pm 0.09	1.64 \pm 0.09	0.580
BMI	23.8 \pm 4.9	26.9 \pm 4.8	0.001
Lower weight	23 (10.6)	1 (1.6)	
Normal weight	118 (54.4)	22 (34.9)	<0.001
Overweight	50 (23)	21 (33.3)	
Obese	26 (12)	19 (30.2)	
Body composition			
Lean body mass	75.9 \pm 10.1	71.4 \pm 9.2	0.001
Fat body mass	24.1 \pm 10.1	28.9 \pm 10	0.001
Albumin (g/dl)			
Moderate depletion	0.5%		
Light depletion	4.3%		0.375
Normal	95.1%	100%	

Continuous variables showed by mean \pm standard variation; BMI: body mass index; Albumin: light and moderate depletion when 2.8–3.4 and 2.1–2.7 g/dl, respectively.

(4.9 versus 0%, $P = 0.375$) and equal proportion of B12 vitamin deficiency (26.3% versus 16.2%, $P = 0.2$).

CD patients showed more anemia (21.7% versus 0%, $P = 0.004$), iron and transferrin saturation depletion (21.7% versus 0%, $P = 0.004$, 29% versus 2.7%, $P = 0.002$, respectively) with equal ferritin levels (13.5% versus 26.7%, $P = 0.1$).

Equal proportions of vitamin D deficiency (36.4% versus 29.7%), insufficiency (38.2% versus 43.3%) and adequacy (25.4% versus 27.0%) in both groups ($P = 0.73$) with a trend to longer term disease duration, with greater vitamin D deficiency (median vitamin D deficiency: 13.85 years versus median sufficiency: 7.45 years) was also observed.

Serum cholesterol level results showed a statistically significant difference between groups (163.9 ± 40.7 mg/dL CD versus 180.7 ± 35.5 mg/dL control; $P = 0.001$), but no difference for the triglyceride levels to groups (121.7 ± 71.8 mg/dL CD versus 100.7 ± 46.7 mg/dL control; $P = 0.4$).

Disease Activity Status (HB index and CRP levels)

Patients in the disease active group showed more overweight and obesity when compared with patients in the remission group (31.8% versus 20.3% and 17.5% versus 9.5%, respectively, $P = 0.024$) and also, the proportion of fat mass 25.7% versus 23.5% was higher in the activity group, with no statistical difference, $P = 0.18$ (Table 3). Patients with previous resection showed less mean BMI 23.1 versus 24.4 ($P = 0.04$). Regarding dietary recall, active patients consumed less fibers (84% versus 74%, $P = 0.06$) and more cholesterol (34% versus 21%, $P = 0.02$), with a weak correlation between CRP levels and cholesterol consumption ($r = 0.19$, $P = 0.006$). No differences in EI for CD patients regarding disease activity or steroids intake. CD patients with disease activity showed low levels of iron, total iron binding capacity (CTLF) and iron saturation, with statistical significance, compared to patients with inactive disease (Table 4).

Discussion

This study's central finding is differences in the intake and nutritional status between CD patients and controls. The former

group showed more underweight and presented increased micronutrient deficiencies for reasons other than intake restrictions. CD patients with disease activity showed more overweight and obesity compared to patients with inactive disease. Recognizing the causes of such deficiencies is primary to improve the nutritional status and avoid deficiencies in IBD patients.

Considering the importance of diet in the etiopathogenesis of IBD, this study also brings a brief review of the literature. As observed, there is a rising incidence of IBD in developing countries that adopt a Westernized lifestyle (17), mainly with high ultra-processed food consumption. Those are made mostly from substances extracted from fats, starches, added sugars and hydrogenated fats (18). Polyunsaturated fatty acids as omega 6 (arachidonic and linoleic acids) are precursors of inflammatory lipid mediators. The ratio omega 6/omega 3 is related to increases in intestinal barrier permeability, dysbiosis and immune activation (19,20). Also, high sugar intake is related to decreased bacterial diversity in the microbiota with fewer species of *Bacteroidetes* and more pathogenic bacteria as *Proteobacteria*, which can promote metabolic endotoxemia via LPS, systemic inflammation and the development of metabolic dysregulation, in addition to providing excess energy (20,21). Although very much focused on experimental studies, emulsifiers, such as carrageenan, carboxymethyl cellulose and polysorbate 80 are mainly associated with intestinal inflammation (22). Those food additives have also been linked to induction of dysbiosis, flare-ups and metabolic syndrome development (23).

Meat intake was mainly associated with the development of ulcerative colitis (UC), with an observed odds ratio of 2.48 (24); however, the literature does not show an appropriate sub-analysis for colonic CD subgroup. Meat contains sulfur amino acid that produces hydrogen sulfide when fermented by bacteria in the gut, compromising the adequate intestinal barrier function and mucus layer (18,24). Regarding CD, high meat consumption might not interfere with a higher risk of symptomatic CD relapse, as reported by FACES study (25). Although the authors concluded that despite a substantial reduction of

Table 3. Nutritional profile according to disease activity

	Disease remission	Disease activity	<i>P</i>
BMI (kg/m ²) (mean \pm SD)	23.4 \pm 4.6	24.8 \pm 5.4	54
Underweight (%)	15 (10.1)	8 (12.7)	
Normal weight (%)	89 (60.1)	24 (38.1)	<0.024
Overweight (%)	30 (20.3)	20 (31.8)	
Obese (%)	14 (9.5)	11 (17.5)	
Body composition			
Lean body mass (%)	76.5 \pm 9.6	74.3 \pm 11.3	182
Fat body mass (%)	23.5 \pm 9.6	25.7 \pm 11.3	181

Table 4. Hemoglobin, iron and B12 vitamin profile according to disease activity

	CRP \leq 3	CRP \geq 3	P
Hemoglobin (g/dL)	13.7 \pm 1.7	13.2 \pm 1.7	0.063
Hematocrit (%)	41.3 \pm 4.4	40.6 \pm 4.7	0.229
MCV (fL)	90.5 \pm 8.1	89.3 \pm 3.7	0.073
Ferritin (ng/mL)	107 \pm 124.6	109.5 \pm 154	0.648
Iron (μ g/dL)	102.3 \pm 44.3	68.8 \pm 43	<0.001
CTLF (μ g/dL)	317.6 \pm 57.1	292.9 \pm 64.5	0.002
Iron saturation	32.2 \pm 13.9	24.5 \pm 15.4	<0.001
B12 vitamin (pg/mL)	524.2 \pm 315	464 \pm 356.4	0.19

Continuous variables arranged by mean and standard deviation

MCV: mean corpuscular volume; CTLF: total iron binding capacity

Normal values:

Hemoglobin: female 12–16 g/dL, male 13–18.1 g/dL; hematocrit: female 35–47%, male 40–52%; VCM: 80–100 fL; ferritin: female 15–150 ng/mL; male 30–400 ng/mL; iron: female 37–145 mg/dL; male 59–158 mg/dL; CTLF: 228–428 mg/dL; iron saturation: 20–40%.

MCV for microcytosis: <80 fL; for macrocytosis: >100 fL.

red meat patients maintained the ingestion, this might have compromised the final results. The PROCID-DCH study (26), a Danish prospective database will reveal the role of diet factors as red meat, processed meat and fiber in the development of autoimmune diseases as CD, UC, psoriasis, psoriatic arthritis, rheumatoid arthritis and multiple sclerosis.

In our study, CD patients consumed more calories due to increased fat and carbohydrate intake. Contrary to these results, Balestrieri et al. (27) summarized that CD patients experience reduced oral intake due to loss of appetite, nausea, vomiting, abdominal pain, diarrhea and also medication side effects, mainly in active disease patients. In our study, almost 70% of the patients were in clinical remission, which may explain this difference.

Literature reports different prevalence rates for micronutrient intake deficiencies for vitamins B1, B3, B6, B12, calcium and iron with no clear disease activity relation. The high UV light exposure in Brazil suggests that Vitamin D deficiency could be related to insufficient dietary intake, once there are not many Vitamin D food sources present in a regular diet (28). In our food analysis, intake revealed 100% of vitamin D inadequacy intake, both in CD patients and controls. This is an alert for physicians who deal with IBD patients in checking Vitamin D levels in subsequent visits. Anemia, the most common systemic IBD complications, was present in 21% of our patients, compatible with the prevalence described in the literature, ranging from 12% to 43%, with notorious iron and B12 vitamin deficiency in patients with clinical activity (29).

Classically, CD is known to promote weight loss but similarly to the general population increasing in weight, these patients may be experiencing a nutritional status transition

phase, especially when they reach an inflammatory control of the disease, mainly in the post-biological era (30). The relation between obesity and CD can be linked to increased visceral fat tissue as demonstrated by Magro et al. (31). Initiation of the inflammatory process in CD is usually triggered in the mesenteric fat contributing to the release of interleukin-6 (IL-6), (IL-1 β) and TNF- α (30,31). The study showed a higher prevalence of overweight and obesity in patients with CD in clinical activity. The meta-analysis published by Singh et al demonstrated that obesity is a predictor of poor response to anti-TNF agents in patients with immune-mediated diseases (32).

Our results showed an excess of body fat and significant overweight and obesity proportions associated with disease activity, with higher consumption of cholesterol and less fiber, similar to other studies (34). As described by Kotze (35), the literature is still controversial about ‘what comes first: the egg or the chicken’. What is known is that obesity is being observed more frequently in IBD outpatient clinics.

Western diets posture cultural practices involving techniques such as food production and processing, and a rich diet in fats and carbohydrates commonly observed for having insufficient or inadequate fiber levels. The intake inability for the recommended daily intake of 25 g of fiber per day can be associated and interrelated with cultural aspects of developing countries such as lack of education access and socioeconomic levels that lie beside a western diet lifestyle (2,19). Our study’s fiber intake was similar between groups, as reported by Filippi et al. (35), even though scoring below recommendations.

In this study, social and physical factors greatly influence low-income CD patients and their diet quality control. Dietary habits and choices have a strong, inverse association between socioeconomic factors such as occupation, income and obesity. The cost of healthy food such as fruits and vegetables is higher than less nutritious, energy-dense food, which might have contributed to the ‘eating mistakes’ observed in this study. Brazilian National Health System did not have the educational skills or economic status to improve diet calorie intake quality. Other studies have also reported 50–69% of patients received little to no information about nutrition and IBD (2).

Patients in remission tend to abstain from certain foods according to beliefs, for example, they withdraw gluten and lactose from their diets thinking these are possible triggers during the flares. This is a modism that might impact vitamin absorption and worse extraintestinal manifestations as osteoporosis. In addition, we recommend that governmental agencies promote not only nutrition-target for IBD, as well as access to healthy food. Recently, the Brazilian Study Group of Inflammatory Bowel Disease (GEDIIB) published a nutritional guide for IBD patients to help prevent the most common triggers to flare-ups. Therefore strategies to lifestyle changes and diet may help prevent the inflammatory onset of the disease.

The multidisciplinary team with an IBD dietitian must work together in educational awareness programs to compel patients about the importance of following a healthy diet, as well as disease prevention campaigns.

This study has some limitations. First, this is a cross-sectional study, which avoids the determination of cause-effect relationships. Second, GLIM criteria for malnutrition were not used as full criteria. Third, the control group's missings who did not fill out the food intake questionnaire might have impacted the final results. Studies with a larger number of patients are necessary to prove the real impact of nutrition disorders on disease burden.

CONCLUSION

The assessment of the intake diet and nutritional status differences between CD patients and controls showed that CD patients were more underweight and had more micronutrient deficiency for reasons other than intake restrictions. Recognizing the causes of such deficiencies is primary to improve the nutritional status and avoid further consequences to IBD patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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