

Original Article

The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab

Roxana Vadan*, Liliana Simona Gheorghe, Alexandrina Constantinescu, Cristian Gheorghe

Center of Gastroenterology and Hepatology, Fundeni Clinical Institute for Digestive Diseases and Liver Transplantation, 258 Fundeni Street, Sector 2, 022328 Bucharest, Romania

ARTICLE INFO

Article history:

Received 20 April 2010

Accepted 24 July 2010

Keywords:

Infliximab

TNF α

Crohn's disease

Nutritional status

Malnutrition

SUMMARY

Background & aims: Malnutrition is variably encountered in adult patients with Crohn's disease. We evaluated the nutritional status at the beginning and during Infliximab treatment in patients with Crohn's disease.

Methods: Patients with moderate/severe flares of disease treated with Infliximab for induction and maintenance of remission were included in a prospective observational study. Body Mass Index and Nutritional Risk Index were calculated in each patient at 0, 6 weeks and then every 8 weeks for one year.

Results: From 30 patients treated with Infliximab 59.3% had low BMI, 35.7% being undernourished. The severity of Crohn's disease did not correlate with low BMI but did correlate with Nutritional Risk Index ($p = 0.001$). In all patients that responded to Infliximab treatment progressive weight gain was observed, all but one patient reaching normal BMI after one year. Mean weight gain was significantly more elevated ($p = 0.001$) and time needed to reach normal BMI was longer in the undernutrition group ($p = 0.01$). Clinical remission was the principal factor associated with weight gain ($p = 0.001$), while there was no influence of endoscopic remission on nutritional status.

Conclusions: In patients with moderate/severe forms of Crohn's disease malnutrition is frequently encountered. Induction and maintenance treatment with Infliximab determines weight gain and corrects malnutrition in all patients with clinical remission.

© 2010 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

1. Introduction

Crohn's disease (CD) is characterized by segmental inflammation of the gastrointestinal tract, most frequently involving the distal small bowel and the colon, and has a fluctuating course, periods of disease activity alternating with periods of remission. Altered nutritional status has been reported in the majority of CD patients, as a result of various mechanisms, depending on the activity of disease. The increased resting energy expenditure is not a major contributor, since it can vary but in general is similar to that in healthy subjects, an intake of 25–30 kcal/kg/day being considered adequate.^{1,2} In remission state the energy and macronutrient needs are usually met, undernutrition being rarely encountered, while in contrast, up to one third of CD patients are reported to be overweight. During remission the most frequent nutritional abnormalities are micronutrient deficiencies, principally resulting from inadequate food intake secondary to dietary restrictions

(reduced milk, fruits, vegetables), sometimes imposed by the physician and sometimes by the patients themselves, driven by the fear of relapse symptoms.^{3,4}

During periods of disease activity, patients usually present with diarrhea, increased intestinal loss and malabsorption. Also food intake is inversely associated with disease's activity and can be significantly reduced due to pain or bowel movement related with meals and also due to nausea, vomiting or loss of appetite. As a consequence, weight loss can be significant, with impact on body mass index, and undernutrition is frequently observed in active CD. Up to 80% of patients with severe flares of disease, especially those hospitalized, are malnourished. The magnitude of malnutrition depends on different factors: extension and location of disease (ileal versus colonic), previous surgery, but the main cause for impaired nutritional status is considered to be the severity of systemic inflammatory response associated with disease flares.⁵

In the last years new, more powerful, agents have been introduced in the therapeutic armamentarium of inflammatory bowel diseases, which by blocking the effects of cytokines that are essential in the inflammatory cascade can control the inflammatory process. Infliximab is a monoclonal chimeric antibody directed against tumor necrosis factor (TNF) α and has been proven efficient

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; TB, tuberculosis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; CDAI, Crohn's disease activity index; BMI, body mass index; NRI, nutritional risk score.

* Corresponding author. Tel./fax: +40 213180455.

E-mail address: roxanavadan@yahoo.com (R. Vadan).

in inducing and maintaining remission in patients with Crohn's disease.^{6,7} As a result of Infliximab treatment, inflammation is down regulated and improvement of disease symptoms and healing of intestinal mucosa are observed in a large percentage of patients.⁸ These actions are expected to have also an effect on the nutritional status of CD patients, by controlling inflammation an improvement of body weight could be obtained in these cases.

Our study aimed to evaluate the changes in nutritional status in patients with CD hospitalized with moderate to severe flares of disease with no or inadequate response to parenteral corticotherapy and which received Infliximab in order to control the acute symptoms and to induce and maintain remission of the inflammatory bowel disease.

2. Methods

2.1. Subjects

Patients included in the study were patients with Crohn's disease with moderate or severe flares of activity, with no or inadequate clinical response to maximal conventional therapy (defined below) admitted at the Gastroenterology Clinic, Fundeni Centre of Digestive Diseases and Liver Transplantation, Bucharest. All patients were treated with Infliximab with the aim to control intestinal disease flare.

The diagnosis of Crohn's disease was made by combining standard biological, endoscopic, histological and radiological criteria. Patients with newly diagnosed as well as with known Crohn's disease were included. In all patients colonoscopy with biopsies and barium follow up for small intestine were available in order to establish the location (small bowel and/or colon) and extension of disease. Patients with fistulizing Crohn's disease were not included in our study. For each patient the following data were noted: demographic data (age, gender, urban or rural residence), smoking status, duration of Crohn's disease, age at diagnosis, number and severity of previous disease flares, concomitant medication for bowel disease, and previous surgery for Crohn's disease. Also the presence of extra intestinal manifestations was noted. Duration and severity of current flare of disease was recorded. For the evaluation of disease's severity, the Crohn's disease activity index – CDAI – was used.⁹ CDAI is a well known index which comprises eight variables: the number of stools, the presence and severity of abdominal pain, the general well being of the patient, the presence of extra intestinal manifestations of disease, the presence of abdominal masses, the use of antidiarrheal drugs and also the presence of anemia and of weight loss. CDAI is a composite score potentially ranging between 0 and 600. In our study patients with CDAI 220–450 were classified as having moderate disease, while patients with CDAI over 450 were considered having severe disease.

All patients received intravenous corticosteroid therapy (metil prednisolone 80 mg daily) with no benefit, or no significant improvement in symptoms after a course of 5–7 days before treatment with Infliximab for induction of remission was considered. In our study treatment with Infliximab was reserved for the corticosteroid resistant patients. Patients did not receive Infliximab treatment if they had symptomatic bowel stenosis, abscesses or any sign of sepsis, cardiac failure, history of lymphoma or multiple sclerosis or any severe associated disease. All patients were screened for tuberculosis by PPD testing and thoracic X ray and also with serum Quantiferon TB Gold test at the beginning of the treatment and also during maintenance Infliximab treatment at 6 months intervals. All tests should have been negative for TB in order to start Infliximab therapy. Before Infliximab treatment the following laboratory studies were done in all patients: hemogram,

biochemistry with liver and kidney function test, including albumin, CRP, ESR. Antibodies against hepatitis C virus, HIV, HBs antigen, antinuclear antibodies were done and patients with positive results were excluded. At each patient visit blood tests were performed: hemogram, biochemical panel including liver function tests, albumin, CRP, ESR.

2.2. Infliximab administration protocol

For induction of remission Infliximab was given as a series of three infusions of 5 mg per kilogram of body weight at weeks 0, 2 and 6. Infliximab (Remicade®, Schering Plough) was administered as a 2 h i.v. infusion in 250 ml of isotonic saline. In patients with response to the induction therapy (defined below) maintenance treatment with Infliximab was started. For maintenance therapy one infusion of 5 mg/kg of body weight was administered at 8 weeks interval. Before Infliximab infusion all patients received an antihistaminic (Loratadine 10 mg 30 min before the start of Infliximab infusion).

2.3. Efficacy evaluation

Six weeks after the first Infliximab infusion the patients were evaluated. Clinical response was defined as a reduction in CDAI of at least 70 points and clinical remission as a value of CDAI of less than 150. The patient was considered nonresponsive if there was no improvement or only a partial improvement in symptoms with a reduction of CDAI of less than 70 points. Also the need for surgical intervention was considered as no response. Only patients with clinical response or remission after induction therapy were received maintenance treatment with Infliximab. During maintenance at each patient's visit CDAI score was calculated and the presence of remission (CDAI of less than 150) or active disease (CDAI above 150) was noted.

Colonoscopy with ileoscopy was performed during maintenance treatment every 24 weeks. Endoscopic remission was defined as absence of ulcerations.

2.4. Nutritional evaluation

At inclusion in the study (at the first Infliximab infusion) and at each patient visit (at week 6 after the first Infliximab dose and than at every 8 weeks interval during maintenance), BMI (body mass index) was calculated based on the height and weight measurements in each patient ($BMI = \text{weight in kilograms} / \text{height in m}^2$). Normal range was considered 20–25 kg/m², obesity > 30 kg/m², borderline underweight 18.5–20 kg/m², undernutrition < 18.5 kg/m².

At inclusion and at 24 weeks and 48 weeks visits during maintenance treatment with Infliximab, NRI was calculated. NRI (Nutritional Risk Index) was calculated as follows: $NRI = 1.519 \times \text{serum albumin (g/L)} + 41.7 \times (\text{current/usual body weight})$.¹⁰ Patients with an NRI > 97.5 were considered not at risk, patients with NRI between 83.5 and 97.5 were considered moderately at risk and those patients with NRI < 83.5 were considered having severe risk by NRI.

2.5. Statistical analysis

Statistical analysis was carried out using the software SPSS for Windows. Data were expressed as mean ± standard deviation and as number or percentage of subjects. Comparisons were conducted using Student's *t*-test and χ^2 test, with statistical significance set for $p < 0.05$. Differences in mean values were tested by one-way analysis of variance (ANOVA) and the Kruskal–Wallis test.

2.6. Ethics

The study design and procedures were approved by our institution ethics committee.

3. Results

30 patients were included in the study. Their characteristics are showed in Table 1.

At the beginning of the study the presence of malnutrition defined by a low BMI was observed in 59.3% of patients, 35.7% of them being undernourished. The presence of undernutrition was not significantly associated with severe flares of disease according to CDAI score. Although the majority of patients with severe disease had low BMI (87.5%) and a great proportion (62.5%) were undernourished, the frequency of malnutrition was high also in the subgroup of patients with moderate disease (47.4% had low BMI and 26.3% were undernourished).

The presence of severe nutritional risk defined by the NRI was observed in 43.3% of patients. The NRI at week 0 had a mean value of 88.58 ± 7.0 and did not differ significantly according to disease location (87.88 ± 7.1 in patients with exclusive colonic involvement compared with 89.61 ± 7.06 in patients with ileocolonic or small bowel CD, $p = 0.53$). At week 0 a significant association was observed between the CDAI score and severe nutritional risk by NRI (Table 2). Weight being a variable in the NRI score, in patients with severe malnutrition (defined by BMI < 18.5) the values of NRI were significantly lower compared with the rest of the patients (Table 4).

The presence of malnutrition at the time of the first Infliximab administration was not related with the duration of disease, location of disease, clinical form (inflammatory or stricturing), and previous treatments. Malnutrition was significantly more frequently encountered in patients in which CD was diagnosed during childhood, before 18 years of age (Table 3).

From the patients treated with Infliximab, 27 (90%) presented a clinical response at week 6 to the biological therapy. All of the responders achieved clinical remission after a mean interval of 20.74 ± 6.75 months, median 22 weeks, and remained in clinical remission during the observation period. The three patients that did not respond were referred for surgical treatment: in two of them a partial colectomy was performed and in the other case a total colectomy was necessary.

All patients that responded at 6 week were observed during one year and in all cases a progressive increase in weight was noted, independent of the BMI value at week 0. All patients gained weight,

Table 2

Frequency of malnutrition in moderate and severe flares of Crohn's disease.

	Severe flares	Moderate flares
BMI < 18.5	5 patients	6 patients
BMI > 18.5	4 patients	15 patients
	$p = 0.16$	
NRI < 83.5	8 patients	5 patient
NRI > 83.5	1 patient	16 patients
	$p = 0.001$	

those with normal BMI as well as those with different grades of undernutrition (Table 4), but the mean weight gain was significantly more elevated in the undernutrition group as compared with those patients with normal or only slightly decreased BMI (borderline underweight), ($p = 0.001$) at 30 weeks and as well at 54 weeks ($p = 0.002$).

The time needed to reach a normal body weight was, as expected, longer in patients with lower values of BMI: 33.4 ± 13.26 weeks in patients with BMI < 18.5 and 18.57 ± 7.8 weeks in patients with BMI > 18.5 ($p = 0.01$).

The rapidity of the response to Infliximab therapy influenced the weight gain: the earlier the clinical remission was obtained, the earlier the weight gain begun and the greater the weight gain at follow up visits, especially in patients who were severely malnourished at the beginning of the treatment. At week 30 weight gain was significantly higher in patients who reached clinical remission earlier (at 14 weeks after the first administration of Infliximab) compared with those who did not ($p = 0.001$) (Fig. 1).

The disappearance of symptoms, respectively the clinical remission was the determinant factor for the improvement in nutritional status for our patients.

There was no influence of the presence or absence of endoscopic remission on the weight gain in our study group (Table 5): the patients with or without endoscopic remission but who were in clinical remission had similar behavior from the nutritional point of view, with consistent weight gain.

As a result of weight gain, after 6 months of maintenance therapy (week 30), only 11.1% of patients were still malnourished, while the great majority (88.9%) had a normal BMI. After one year of therapy only one patient (3.7%) had still a low BMI, but being only borderline underweight.

NRI at week 30 was >97.5 (patients were not at risk) in 74.1% of cases and only slightly decreased (moderate risk) in the rest of the patients. Mean NRI at week 30 was 99.62 ± 2.54 . No cases of persistent nutritional risk were observed at week 52 (mean NRI at week 52 was 100.12 ± 2.24). No significant differences in NRI were observed during Infliximab treatment at week 30 and week 52 between patients with or without malnutrition at week 0.

The weight gain had economic implications since in 8/27 patients (29.6%) in order to maintain the dose of Infliximab per kg body weight, an increased number of vials had to be administered.

When asked about food habits, patients reported increased appetite, increased tolerance to food, increased quantity of food ingested, so the gain in weight in our group of patients appears to

Table 1

CD patients' characteristics.

Age: mean (min–max)	33.3 ± 13.87 (18–60) years
Sex Nr (%)	17 (56.7%) males 13 (43.3%) females
Mean time since diagnosis of Crohn's disease (min–max)	5.03 (0–20) years
Disease location	
Ileum % (N)	3.3% (1)
Colon % (N)	63.3% (19)
Ileum + Colon % (N)	33.3% (10)
Disease behavior	
Inflammatory % (N)	60% (24)
Stricturing % (N)	40% (6)
Therapies	
Previous corticotherapy % (N)	76.7% (23)
Previous Infliximab % (N)	23.3% (7)
Current Azathioprine % (N)	56.7% (17)
Previous surgery % (N)	43.3% (13)
Smoking (previous or actual) % (N)	3.3% (1)
Extra intestinal manifestations % (N)	20% (6)

Table 3

Risk factors for malnutrition in patients with active Crohn's disease.

Location of disease (colonic or ileocolonic)	$p = 0.16$
Behavior of disease (stricturing or inflammatory)	$p = 0.25$
Age at diagnosis (less than 18 years)	$p = 0.003$
Extra intestinal manifestations	$p = 0.11$
Previous surgery	$p = 0.13$
Previous Infliximab	$p = 0.62$
Previous Azathioprine	$p = 0.12$
Previous corticosteroids	$p = 0.34$

Table 4

Changes in weight, BMI and NRI for the patients with response to Infliximab therapy in the groups with and without severe malnutrition at week 0.

Week 0 BMI	<18.5	>18.5
Mean BMI at week 0	17.31 ± 1.22 (14.9–18.4)	21.03 ± 2.1 (19.6–27.2)
Mean BMI at week 30	21.01 ± 1.69 (18.7–24.4)	23.24 ± 2.27 (20.7–28.3)
Mean weight gain at week 30	8.5 ± 3.2 (4–13) <i>p</i> = 0.001	4.29 ± 1.35 (2–6)
Mean BMI at week 54	21.46 ± 1.61 (19.3–25.2)	23.51 ± 2.22 (20.7–28.3)
Mean weight gain at week 54	11.2 ± 3.58 (7–17) <i>p</i> = 0.002	6.58 ± 2.32 (4–12)
Mean NRI at week 0	84.97 ± 5.03 (78.8–96) <i>p</i> = 0.001	93.84 ± 6.18 (85.5–99.8)
Mean NRI at week 30	99.1 ± 3.47 (93–104) <i>p</i> = NS	99.94 ± 1.85 (96–103)
Mean NRI at week 54	99.8 ± 2.65 (97.6–105) <i>p</i> = NS	100.42 ± 2.18 (99–105.6)

be the result of the increased intake of normal food, since none of our patients received enteral nutrition supplements (sip feeding or enteral nutrition).

4. Discussion

The altered nutritional status of patients with inflammatory bowel diseases was previously recognized and extensively studied in pediatric patients, in this group the impact of malnutrition being most important due to its effect on linear growth and pubertal development.^{11,12} For adult patients with IBD there are fewer data regarding the prevalence of nutritional impairment and also the influence of therapy on nutritional parameters, especially for the newest therapeutic modalities, such as biologic agents.

Our study evaluated the prevalence of malnutrition and the influence of Infliximab therapy in a group of patients with moderate/severe flares of Crohn's disease.

Malnutrition (BMI under 20) was observed in 59.3% of patients, being severe (BMI < 18.5) in 35.7% of patients. The frequency of malnutrition in our group is high compared with the prevalence of malnutrition generally reported in hospitalized patients with Crohn's disease,¹³ but depending on the method of evaluation, values up to 80% can be expected in patients with active disease.⁵

The severity of Crohn's disease flares appreciated by CDAI score did not correlate with the presence or the increased severity of malnutrition, there was no significant difference in the nutrition status between patients with moderate and severe flare of disease. We must acknowledge that even if CDAI score classified our patients as having moderate or severe disease, all of them had a high inflammatory activity revealed by the lack of response to the

treatment with parenteral corticosteroids. Also, all our patients reported weight loss at inclusion, and even if its magnitude did not always determine a drop in BMI sufficient to classify the patient as malnourished/undernourished, in some cases the weight loss was significant. The lack of correlation between CDAI and severity of malnutrition can also be explained by the high frequency of malnutrition in the subgroup of patients with moderate disease. The evaluation of patients by NRI (Nutritional Risk Index), which takes into consideration the current weight compared with usual body weight and also the albumin levels, revealed a significant association between severe risk as appreciated by NRI and severe disease as appreciated by CDAI. A high rate of complications during hospital stay and after surgical interventions was reported and is to be expected in NRI defined severely at risk patients.^{14,15} Patients with severe flares of Crohn's disease are consequently at high risk of being severely malnourished and need special nutritional evaluation, not only by BMI. In these patients, with the aim of improving prognosis, prompt nutritional intervention is mandatory since if the control of symptoms is not achieved by medical therapy surgery is to be expected.

In our study, the presence of malnutrition at inclusion was not influenced by disease location, behavior, and previous medical or surgical therapies. We expected a higher frequency of severe malnutrition in patients with concomitant small bowel involvement as compared with strict colonic location of disease, assuming that malabsorption resulting from the presence of small bowel lesions will impact further on patient's weight, but in our group of patients disease location did not influence the nutritional status. Previous reports showed a lower body mass index in patients with small bowel involvement, but the patients that were evaluated were in inactive state.¹⁶ Probably in our patients the most important factor that induced weight loss and consequently malnutrition was the activity of disease.

The only parameter significantly associated with the presence of malnutrition at inclusion was the age at diagnosis: patients diagnosed with Crohn's disease in childhood were more frequently malnourished as compared with patients with later onset of disease. All our patients diagnosed with Crohn's disease at less than 18 years of age were still young when included in the present study,

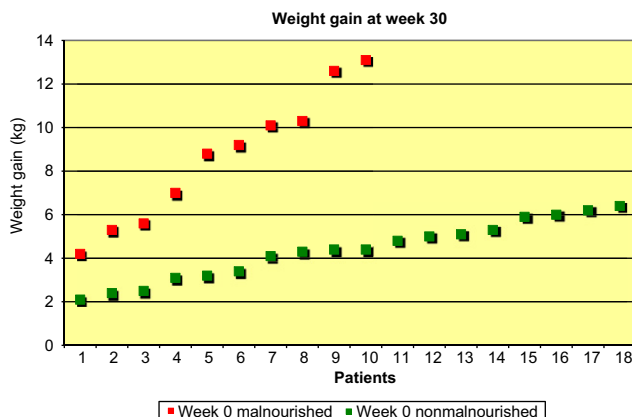


Fig. 1. Weight gain at week 30 in patients with and without malnutrition at week 0.

Table 5

Weight gain in patients with and without endoscopic remission.

	Yes	No	<i>p</i>
<i>Endoscopic remission at week 30</i>			
Weight gain at week 30	6.25 ± 3.01	5.53 ± 3.04	0.54
Weight gain at week 52	8.75 ± 3.86	7.93 ± 3.45	0.52
<i>Endoscopic remission at week 52</i>			
Weight gain at week 30	6.09 ± 2.99	4.8 ± 3.11	0.24
Weight gain at week 52	8.68 ± 3.77	6.6 ± 2.19	0.31

all of them being under 25 years old. The impact of disease on nutritional status was in our group of patients' age dependent, although other studies did not show a difference in the prevalence of malnutrition between adult and pediatric patients.¹⁷ In our experience young patients, with early onset CD were the more prone to develop malnutrition associated with a flare of disease. The greater impact of disease activity on nutritional status in young patients could be explained by the reduced lean body mass and fat mass reported in these patients.^{18,19}

The great majority of our patients (90%) responded to the induction treatment with Infliximab, obtaining a clinical response at week 6, which was followed in all of them by clinical remission after variable time periods (median 22 weeks). In responders a progressive weight gain was observed, regardless of the presence or absence of malnutrition at the beginning of treatment. Not only malnourished patients had weight gain but also patients with normal BMI at inclusion. The weight gained by malnourished patients was significantly greater compared with the rest of the patients. In one third of patients, as a result of weight gain an increased quantity of Infliximab was needed, with impact on treatment cost. After Infliximab treatment all patients achieved a normal BMI, the time needed for this being significantly longer in severely malnourished patients, as expected since in this group the amount of weight gained was greater.

The time patients needed to reach clinical remission influenced the nutritional status: the earlier clinical remission was obtained, the sooner the patient's weight began to increase and during maintenance treatment, at week 30, the weight gain was significantly greater in early responders. From our clinical observations resulted that weight gain was determined by increased appetite and increased food intake, both related with improvement of symptoms and of general well being associated with clinical remission determined by Infliximab treatment. The clinical remission was the most important factor influencing the nutritional status in our patients, while the presence or absence of endoscopic remission did not change the weight gain.

Which is the mechanism by which Infliximab exerts its effect on nutritional status is still a matter of debate. A double action could be involved in patients with inflammatory bowel diseases: an anti cytokine action and a clinical effect determined by the control of disease's activity. TNF α , previously known as cachectin- α is a mediator of inflammation-induced cachexia²⁰ and presumably its blocking (at plasma and membrane receptor levels) by Infliximab could enhance appetite and promote weight gain. In the last years the role of leptin and adiponectin in regulating food intake was demonstrated: increased leptin induces anorexia and reflects adipose tissue mass.²¹ Infliximab influence on serum leptin levels is contradictory: increased levels, decreased levels and no changes were reported.^{22–25} Regardless of its mechanism of action, the effect of Infliximab of promoting weight gain was demonstrated in patients with psoriasis²⁶ and spondyloarthropathy, presumably as a result of increased fat mass.²⁷ In the present study, Crohn's disease patients with clinical remission induced by Infliximab continued to present weight gain during maintenance treatment. In our opinion, in IBD patients during flares of disease weight gain associated with Infliximab treatment is mainly determined by control of inflammation and subsequent improvement in symptoms, while during periods of remission a direct effect of Infliximab on fat mass and body weight control mechanisms can contribute.

In conclusion, in patients with moderate to severe forms of Crohn's disease malnutrition is frequently encountered. Induction and maintenance treatment with Infliximab determines weight gain and corrects malnutrition in all patients with clinical remission.

Conflict of Interest

None.

Acknowledgements

Statement of authorship: RV was involved in the conception and design of the study, the collection of data and drafted the manuscript. LG was involved in the conception of the study and collection of data. AC was involved in collection of data and statistical analysis. CG was involved in the conception of the study and critically appraisal of the manuscript.

References

- Sasaki M, Johtatsu T, Kurihara M, Iwakawa H, Tanaka T, Tsujikawa T, et al. Energy metabolism in Japanese patients with Crohn's disease. *J Clin Biochem Nutr* 2010;**46**(1):68–72.
- Aghdassi E, Wendland BE, Stapleton M, Raman M, Allard JP. Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. *J Am Diet Assoc* 2007;**107**(9):1575–80.
- Filippi J, Al-Jaouni R, Wiroth JB, Hébuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. *Inflamm Bowel Dis* 2006;**12**(3):185–91.
- Sousa Guerreiro C, Cravo M, Costa AR, Lourdes Tavares AM, Moura-Santos P, Marques Vidal P, et al. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. *Am J Gastroenterol* 2007;**102**(11):2551–6.
- Van Gossum A, Cabre E, Hébuterne X, Jeppesen P, Krznaric Z, Messing B, et al. ESPEN guidelines on parenteral nutrition: gastroenterology. *Clin Nutr* 2009;**28**(4):415–27.
- Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. Crohn disease cA2 Study Group. A short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. *N Engl J Med* 1997;**337**(15):1029–35.
- Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002;**359**(9317):1541–9.
- D'Haens G, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 1999;**116**(5):1029–34.
- Best WR, Becktel JM, Singleton JW, Kern Jr F. Development of a Crohn's disease activity index. *Gastroenterology* 1976;**70**(3):439–44. National Cooperative Crohn's Disease Study.
- Buzby GP, Knox LS, Crosby LO, Eisenberg JM, Haakenson CM, McNeal GE, et al. Study protocol: a randomized clinical trial of total parenteral nutrition in malnourished surgical patients. *Am J Clin Nutr* 1988;**47**(Suppl. 2):366–81.
- Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut* 1993;**34**(7):939–43.
- Savage M, Beattie R, Camacho-Hubner C, Walker-Smith JA, Sanderson IR. Growth in Crohn's disease. *Acta Paediatr* 1999;**88**(428):89–92. Suppl.
- Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflamm Bowel Dis* 2008;**14**(8):1105–11.
- Buzby GP, Williford WO, Peterson OL, Crosby LO, Page CP, Reinhardt GF, et al. A randomized clinical trial of total parenteral nutrition in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on protocol design. *Am J Clin Nutr* 1988;**47**(2):357–65. Suppl.
- Naber TH, Schermer T, de Bree A, Nusteling K, Eggink L, Kruimel JW, et al. Prevalence of malnutrition in nonsurgical hospitalized patients and its association with disease complications. *Am J Clin Nutr* 1997;**66**(5):1232–9.
- Capristo E, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. *Am J Gastroenterol* 1998;**93**(12):2411–9.
- Marcil V, Bucionis V, Bitton A, Szilagyi A, Serban D, Levy E, et al. Malnutrition in adults and children with IBD: is there a difference? *Am J Gastroenterol* 2009;**104**(Suppl. 3):S550.
- Capristo E, Mingrone G, Addolorato G, Greco AV, Gasbarrini G. Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. *J Intern Med* 1998;**243**(5):339–47.
- Burnham JM, Shults J, Semeao E, Foster BJ, Zemel BS, Stallings VA, et al. Body-composition alterations consistent with cachexia in children and young adults with Crohn disease. *Am J Clin Nutr* 2005;**82**(2):413–20.
- Argilés JM, López-Soriano J, Busquets S, López-Soriano FJ. Journey from cachexia to obesity by TNF. *FASEB J* 1997;**11**(10):743–51.
- Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. *Cell* 2001;**104**(4):531–43.
- Franchimont D, Roland S, Gustot T, Quertinmont E, Toubouti Y, Gervy MC, et al. Impact of infliximab on serum leptin levels in patients with Crohn's disease. *J Clin Endocrinol Metab* 2005;**90**(6):3510–6.

23. Fawcett RL, Waechter AS, Williams LB, Zhang P, Louie R, Jones R, et al. Tumor necrosis factor- α inhibits leptin production in subcutaneous and omental adipocytes from morbidly obese humans. *J Clin Endocrinol Metab* 2000;**85**(2):530–5.
24. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Kouroumalis EA. The effect of infliximab on circulating levels of leptin, adiponectin and resistin in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2007;**19**(9):789–94.
25. Derdemezis CS, Filippatos TD, Voulgari PV, Tselepis AD, Drosos AA, Kiortsis DN. Effects of a 6-month infliximab treatment on plasma levels of leptin and adiponectin in patients with rheumatoid arthritis. *Fundam Clin Pharmacol* 2009;**23**(5):595–600.
26. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor- α therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2008;**22**(3):341–4.
27. Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthritis receiving anti-tumor necrosis factor- α treatment. *J Rheumatol* 2008;**35**(5):855–61.