Digestive and Liver Disease 49 (2017) 495–499

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Nutritional status and bioelectrical phase angle assessment in adult Crohn disease patients receiving anti-TNFα therapy

Sara Emerenziani[a,*], Livia Biancone[b], Michele Pier Luca Guarino[a], Paola Balestrieri[a], Elisa Stasi[b], Mentore Ribolsi[a], Maria Paola Rescio[a], Annamaria Altomare[a], Silvia Cocca[a], Francesco Pallone[b], Michele Cicala[a]

[a] Unit of Digestive Disease of Campus Bio Medico University of Rome, Italy
[b] Department of Systems Medicine, Università "Tor Vergata" of Rome, Italy

ARTICLE INFO

Article history:
Received 19 August 2016
Received in revised form
16 December 2016
Accepted 22 December 2016
Available online 30 December 2016

Keywords:
Biologic and conventional therapies
Body composition
Crohn's disease
Malnutrition
Nutritional status

ABSTRACT

Background: Altered body composition is frequently observed in Crohn's disease (CD) patients.
Aims: To investigate the nutritional status, and the effect of different therapeutic regimes in adult CD patients.
Methods: Fat free mass (FFM) and BIA-derived phase angle (PhA) were assessed in 45 CD patients, 22 on conventional therapy (CT) and 23 on maintenance therapy with infliximab (MT). Nutritional status was also assessed in 12 CD patients before and following the induction protocol with infliximab. BIA data of CD patients were compared with those of 20 healthy asymptomatic volunteers. In CD patients C Reactive Protein (CRP) and albuminaemia dosage were obtained.
Results: The mean values of PhA and of FFM were significantly lower in CT patients when compared with control group and MT patients. Following infliximab treatment FFM increased, although not significantly, while mean phase angle value significantly increased from 4.6 ± 0.3 to 6.2 ± 0.4 ($p < 0.05$). CRP was significantly lower in MT patients compared to that in CT patients.
Conclusion: CD patients on conventional therapy showed a lower FFM and a lower mean phase angle score compared to those on infliximab therapy. Following infliximab treatment the mean phase angle score normalized. PhA is a reliable nutritional indicator in IBD patients and could be considered as an additional tool for assessing response to treatment.
© 2016 Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

1. Introduction

Malnutrition is a common challenge in patients with inflammatory bowel disease (IBD), particularly in patients with active Crohn's disease (CD) [1,2]. In these patients, several factors such as small bowel involvement, multiple intestinal resections, diarrhea, malabsorption, inadequate food intake, pain, nausea and vomiting may be all involved in developing malnutrition [3,4]. Nevertheless, the main cause of impaired nutritional status is considered to be the severity of the systemic inflammatory response associated with disease flares [5]. A recent systematic review has pointed out that nearly one-third of CD patients has altered body composition, characterized by reduced body mass index (BMI), fat free mass (FFM) and fatty mass (FM), compared with healthy subjects, despite only 5% of them are underweight when using BMI criteria alone [6]. Indeed, routine clinical assessment of IBD patients, using anthropometric techniques such as BMI, may provide an inaccurate assessment of body composition, and an under-recognition of malnutrition. The bioelectrical impedance analysis (BIA) is a simple, non-invasive, and reproducible technique which quantitatively evaluates body composition [7]. BIA does not measure body composition directly but, rather, it assesses body resistance (R) and reactance (Xc) and combines these factors with anthropometric variables (weight and height), sex, and age to estimate body compartments using prediction equations. Moreover, BIA-derived phase angle (PhA) is a variable obtained from the relationship between R and Xc and seems to be promising as a new nutritional indicator [8]. Findings from previous studies clearly indicate that PhA is a good prognostic tool in several diseases and, in large series of patients with gastrointestinal diseases, malnourished patients were characterized by a significantly lower mean PhA value compared to well-nourished patients affected by the same disease [9,10]. More recently, the phase angle has been assessed in pediatric IBD patients during clinical remission [11]. This study has shown

* Corresponding author at: Department of Digestive Disease of Campus Bio Medico University of Rome, via Alvaro del Portillo 200, 00100 Roma, Italy. Fax: +39 0622541456.
E-mail address: s.emerenziani@unicampus.it (S. Emerenziani).

http://dx.doi.org/10.1016/j.dld.2016.12.026
1590-8658/© 2016 Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

a low phase angle value and a reduced lean body mass in patients compared to controls. Hence, PhA could be considered a reliable prognostic marker and should be used for nutritional assessment and monitoring.

In the last decade, recent development of treatments with biologic agents has allowed a better and sustained control of mucosal inflammation. Infliximab is a monoclonal chimeric antibody against tumor necrosis factor-alfa (TNF), proven to be very efficient in inducing and maintaining remission in patients with Crohn's disease and Ulcerative Colitis [12,13]. When compared to conventional therapies such as steroids and immunosuppressant, infliximab treatment allows a sudden and sustained down regulation of inflammation and the mucosal healing can now be observed in the vast majority of patients within one year of treatment. These effects are expected to impact nutritional status in CD patients, in a short period of time.

The aim of the present study was to compare the nutritional status by means of BMI, FFM and of BIA derived phase angle in CD patients undergoing conventional therapies and infliximab therapy (comparative study). In another group of consecutive patients, the assessment of nutritional status was performed before and after the induction protocol with infliximab (follow-up study). Data were compared to those obtained from a healthy control group.

2. Methods

2.1. Subjects

2.1.1. Comparative study

In order to evaluate the effect of different treatments on nutritional status we compared fat free mass and BIA-derived PhA in consecutive CD patients on conventional treatment and on infliximab therapy attending the Department of Gastroenterology at Campus Bio Medico and at Tor Vergata University of Rome (from January 2013 to January 2014). BIA analysis was performed in all subject at enrollment. Patients who reported intense physical activity, alcohol and fluid intake before the evaluation, state of dehydration or water retention, use of diuretics were not enrolled in the study as all these factors are known to impair BIA analysis. Another exclusion criteria was fistulazing pattern of CD disease as the main indication of treatments. The diagnosis of CD was determined by the combination of clinical, endoscopic, histological and radiological criteria [14].

2.1.2. Follow-up study

To assess the effect of infliximab therapy on nutritional status, a different group of thirteen CD patients, consecutively attending the Department of Gastroenterology at Campus Bio Medico and at Tor Vergata University of Rome (from June 2013 to January 2014), were enrolled for the follow-up study. BIA analysis was performed in all patients before and after scheduled infliximab induction protocol (Remicade; Centocor Inc., Malvern, PA, USA) at a dose of 5 mg/kg (at weeks 0, 2, 6). Indications for infliximab treatment were: disease severity, steroid dependent disease (unable to reduce steroids below the equivalent of prednisolone 10 mg/day without recurrent active disease or relapse within 3 months of stopping steroids) and steroid refractory (active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks), as well as steroid contraindications (i.e. uncontrolled hypertension or diabetes, severe osteoporosis, mood disturbance). Exclusion criteria were: cancer or history of cancer, pregnancy, chronic heart failure, previous tuberculosis, presence of intestinal strictures or abscesses, active metabolic disorders such as thyroid disorders, and malignant obesity. All patients were allowed to take concomitant therapies such as 5-aminosalycilates, immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate), antibiotics and steroids. Crohn's Disease Activity Index (CDAI), assessment of body composition and BIA derived PhA were evaluated in all patients at inclusion in the study (immediately before the first infliximab infusion) and before the first infusion of the maintenance period (12 ± 2 weeks following the first infusion).

For each patient of the two study groups the following data were recorded: demographic data (age, gender and ethnicity), smoking status, duration of Crohn's disease, concomitant medications and previous surgery for Crohn's disease. Blood samples were collected for C Reactive Protein (CRP) as a marker of inflammation and albuminaemia. Hypoalbuminaemia was defined as albumin levels lower than 3.5 g/dL.

BIA data of all CD patients were compared with those of 20 healthy asymptomatic volunteers enrolled among hospital staff (13 men, median age 47 years, range 31–57) (healthy control group). The study protocol was approved by the Ethics Committee of the Campus Bio-Medico of Rome and all the examined subjects completed a written informed consent to participate in the study.

2.2. Analysis of data

2.2.1. Clinical assessment of disease activity

CDAI is a composite score potentially ranging between 0 and approximately 600. In our study, according to standardized criteria, patients were classified as having disease in remission if presenting a CDAI score below 150, mild disease if ranging from 150 to 220, moderate disease if ranging from 220 to 450 and severe disease was defined as a value greater than 450 [15]. In the patients enrolled in the follow-up study, a good clinical response was defined as a $\geq$70 point reduction in CDAI score and clinical remission was defined as a CDAI $\leq$150. Patients were considered non responsive if there was no improvement or only a partial improvement in symptoms with a reduction of CDAI <70 points.

2.3. Nutritional evaluation

Weight and height were measured using an electronic weighing scale with a coupled anthropometer (Seca 799; Italy). Body mass index was calculated by dividing total body weight (in kilograms) by the squared height (in meter squared) and classified according to the criteria of the World Health Organization [16]. According to the standardized criteria, patients were grouped into well nourished (BMI, 18.5–24.5), underweight or malnourished (BMI $\leq$ 18.5) and overweight (BMI $\geq$ 25).

Tetrapolar BIA was performed using a calibrated Biodynamics portable equipment, model 310 (Seattle, USA), which applies a current of 800 μA and a single frequency of 50 kHz. Measurements were taken early in the morning, when patients had been fasting for at least 4 h. Bioelectrical impedance analysis was conducted with patients lying supine on a bed with legs apart and arms not touching the torso. Resistance (R) and reactance (Xc) were directly measured in ohms. BIA derived angle phase was calculated by a dedicated software (Bodygram PRO 3.0). The phase angle alpha is a raw value and indicator of body cell mass and FFM is calculated using equations/algorithms which are also based on the phase angle alpha. The body composition was assessed measuring FFM in kilograms and cut-off values of phase angle were derived by mean and standard deviation reference values resulting from our healthy control group.

2.4. Statistical analysis

Descriptive statistics (means and SDs) were used to describe key clinical and demographic characteristics. Differences between groups were analyzed with Unpaired t-test. ANOVA analysis of vari-

Table 1
Clinical characteristics of patients.

	Conventional therapy	Biological therapy	p
No. of patients	22	23	
Gender (F)	12 (54%)	13 (52%)	*n.s.*
Age (mean ± SD)	40 ± 11	47 ± 14	*n.s.*
Disease duration year (mean ± SD)	12 ± 3	11 ± 2	*n.s.*
CDAI < 150 (%)	20	42	p < 0.05
CDAI 150–220 (%)	50	23	
CDAI 150–450 (%)	15	25	
Ileocolonic involvement (%)	79	73	*n.s.*
Previous surgery (%)	50	63	*n.s.*
Smoking (%)	27	35	*n.s.*

ance was used to compare quantitative data among three groups (controls, patients on conventional therapy, patients on biological therapy). The comparison of the variables before and after the treatment was performed using the paired t-test. A p value < 0.05 was considered as significant.

3. Results

3.1. study population

3.1.1. Comparative study

Out of 63 eligible patients, 10 patients did not agree to participate in the study and 8 were excluded due to exclusion criteria (2 because of concomitant use of diuretics, 6 because of presence of perianal penetrating more than intestinal inflammatory disease). A total of 45 Caucasian adults affected by CD (25 F, mean age 44 ± 14) were enrolled. Of these, 22 (12 F, mean age 40 ± 11) were on conventional therapy (mean duration at enrollment 8 months, ranges 6–11 months) and 23 (13 F, mean age 47 ± 14) on therapy with infliximab treatment (mean duration 7 months, ranges 6–10 months). Baseline demographic and clinical data of the population of the comparative study are summarized in Table 1. Age, gender and BMI did not differ between patients excluded from the study and the study population.

No significant differences between patients undergoing conventional or infliximab therapy, in terms of age, average duration of disease, ileo-colonic involvement, presence of one or more surgical procedures during the disease, association of conventional or infliximab therapy with steroids and smoker habit, were observed. On the other hand, patients belonging to the group on infliximab therapy were characterized by a higher percentage of disease in remission phase compared to those on conventional treatment. None of the patients showed a CDAI score >450. Data concerning body composition and analysis of BIA derived PhA are reported in Table 2.

Table 3
Baseline demographic and clinical data of the outcome study patients.

No. of patients	12
Gender (F)	5/12 (41%)
Age (mean ± SD)	45 ± 8
Disease duration years (mean ± SD)	4 ± 2
CDAI 220–450	7/12 (58%)
CDAI > 450	5/12 (41%)
Steroid therapy	5 (41%)
Ileal involvement (%)	9 (75%)
Previous surgery (%)	4 (33%)
Smoking (%)	3 (25%)

BMI value did not differ between groups. The FFM was significantly increased in patients on infliximab therapy compared to patients on conventional therapy, both in males and females. The mean value of PhA was significantly lower in patients on conventional therapy compared to that in patients on infliximab therapy, both in males and females. Patients on conventional therapy showed a significantly lower FFM and mean value of PhA compared to that of controls (Table 2). ANOVA analysis of variance confirmed a significant difference among the three groups (controls, patients with conventional therapy, patients with infliximab therapy) in terms of FFM and mean PhA value, both in males and females (p< 0.001 and p < 0.01 respectively).

The mean value of CRP was significantly lower in patients on infliximab therapy compared to that in patients on conventional therapy (6.6 ± 5.3 *vs* 2.2 ± 1.9 respectively; p < 0.04). No significant difference was observed concerning albumin level between the two groups (3.91 ± 0.6 *vs* 4.01 ± 0.6 respectively; p = *ns*)

3.2. Follow-up study

Clinical characteristics of the 12 patients included in the follow-up study (4 women, average age of 45 ± 8), are shown in Table 3. All patients, except one, showed a satisfactory clinical response at week 6 to infliximab therapy. One patient, not responding to infliximab, underwent surgery and was therefore excluded from the study.

FFM increased, although not significantly, from a mean of 41.7 ± 3.7 to a mean of 44.6 ± 4.2 following the induction protocol (Table 4). Mean phase angle value significantly increased from a mean of 4.6 ± 0.3 to a mean of 6.2 ± 0.4 (p < 0.05), being increased after the induction protocol in all patients except one.

The mean value of CRP significantly decreased following the infliximab induction protocol (10.6 ± 7.3 *vs* 3.4 ± 2.4 respectively; p < 0.05). The mean albumin increased, although not significantly, following the induction protocol (3.1 ± 0.5 *vs* 4.06 ± 0.8 respectively; p:*ns*).

Table 2
Body composition and PhA analysis in patients receiving conventional *vs* biological therapy.

	Control group	Conventional therapy	Biological therapy	p
Men	(n = 13)	(n = 10)	(n = 10)	
BMI (mean ± SD)	23.1 ± 0.9	21.9 ± 2.0	22.8 ± 3.2	
FFM kg (mean ± SD)	58 ± 6.3	52,08 ± 3.3°°	58 ± 5.1**	**p < 0.05
PhA (median ± SD)	6,7 ± 0,8946	5,6 ± 1,265°	7,1 ± 1,218*	*p < 0.05
Women	(n = 7)	(n = 12)	(n = 13)	
BMI (mean ± SD)	21.9 ± 1.5	21.6 ± 1.3	22.8 ± 3.7	
FFM kg (mean ± SD)	47 ± 3.6	40,55 ± 4.2°°	46.4 ± 4.3**	**p < 0.05
PhA (median ± SD)	6,4 ± 0,9429	5,2 ± 1,717°	6,6 ± 0,9531*	*p < 0.05

** p < 0.01 *vs* conventional.
* p < 0.05 *vs* conventional.
°° p < 0.01 *vs* control group.
° p < 0.05 *vs* control group.

Table 4
FFM and BIA derived phase angle before the first infusion and following the induction protocol with infliximab (12 ± 2 weeks from the first infusion).

Patients	FFM		Phase angle	
	Baseline	Following induction protocol	Baseline	Following induction protocol
IM	39.4	43.2	7.8	7.6
BM	36.1	38.3	4.2	6.1
EP	47.2	51.6	4.0	7.6
MC	42.4	44.0	5.8	8.2
NG	46.4	49.8	6.1	6.2
ED	44.3	47.2	5.2	6.8
AT	41.5	45.2	4.3	6.0
AM	39.5	41.3	5.5	6.9
CP	40.2	40.9	5.8	6.1
MS	38.6	41.2	4.4	6.5
ST	38.2	39.5	5.1	6.9
MN	41.3	42.5	5.7	6.4
Mean ± SD	41.7 ± 3.7	44.6 ± 4.2	4.6 ± 0.3	6.2 ± 0.4*

* $p < 0.05$ *vs* baseline.

4. Discussion

Nutritional status evaluation should be one of the first steps for a successful management of acute and chronic gastrointestinal diseases, mainly of IBD. Although the widespread clinical awareness strongly suggests that the assessment of nutritional status in patients with CD may improve clinical outcomes by limiting disease complications and hospitalization, few data are available regarding the impact of nutritional impairment in these patients. Moreover, to our knowledge, no controlled studies investigating the impact of biologic therapies on nutritional status are available. Our study evaluated the fat free mass and the BIA-derived phase angle in an adult series of patients with Crohn's disease undergoing maintenance treatments, either with conventional or biologic agents. In the present study the role of infliximab treatment on nutritional status was investigated in a prospective manner: findings from our series showed that patients on conventional therapy were characterized by a significantly lower FFM and mean values of BIA-derived phase angle as well as by higher CRP values when compared to that on infliximab therapy. These findings further support the key role of the disease activity and mucosal-systemic inflammation in determining the impairment of nutritional status, which is also associated with a lower FFM. Findings from our patients belonging to the follow-up study show that after the induction protocol with biologic therapy there was a significant improvement of nutritional parameters. Indeed, following the induction regimen with infliximab, the fat free mass increased, although not significantly, and the mean value of BIA-derived phase angle, which was significantly lower at enrollment, increased significantly, reverting to the normal range of our healthy control group in almost all patients. Although the precise mechanism of action of infliximab on nutritional status is still a matter of debate, the improvement recorded following a relatively short period of therapy with infliximab (induction period) seems to be mainly determined by the suppression of mucosal inflammation as demonstrated by a significant reduction of CRP values. Supporting this hypothesis, it is well known that the inflammation-induced cachexia is mediated by TNF-alfa and other cytokines by acting both at membrane and receptor levels [17–19].

In agreement with the literature, results of the FFM and BIA-derived phase angle values in our series show that the assessment of BMI, as a standard marker of nutritional status, is not sufficient to detect the presence of malnutrition in IBD patients [6]. A recent study conducted on 94 CD patients in clinical remission, has shown that 74% of these patients, considered well-nourished according to BMI and serum albumin values, when evaluated with BIA showed a significantly reduced value of body cell mass (BCM), with a consequent reduction in free fatty mass [20]. In that study, no data concerning the BIA-derived phase angle were provided. This discrepancy between BMI values and data derived from assessment of body composition by means of BIA should not be underestimated in the clinical evaluation of IBD patients. In our study, in CD patients on conventional therapy a reduced FFM was observed despite normal value of BMI, thus suggesting the need of an early appropriate nutritional screening. Indeed, it has been demonstrated that worsening of nutritional status and malnutrition have well known adverse effects on the clinical outcome and on quality of life [9,21]. Several methods can be employed to measure body composition. Although the BIA technique does not provide a direct measurement of FFM in comparison to dual energy x-ray emission (DEXA), it allows a sensitive and not invasive estimation of the body composition. The accuracy of BIA may be limited by several factors such as intense physical activity, alcohol and fluid intake before the evaluation, state of dehydration or water retention, use of diuretics. None of the above mentioned factors were present in the patients enrolled in the present study. Moreover, none of our patients showed acute body mass change prior to study enrollment, a marker known to be a limitation of the use of BIA. Since there is still no agreement on the cut off levels to be used for phase angle evaluation, in line with previous literature, for our analysis we utilized the mean phase angle scores of the healthy control group. There is a clear need to define optimal thresholds of phase angle as indicators of nutritional status. Nevertheless, until now BIA derived phase-angle represents the most clinically established impedance parameter and it might be considered as a reliable and optimal marker of nutritional status [8]. Possible limitation of our follow-up study are the relatively small sample size and the lack of dietary and physical activity data. Indeed, the effect of the infliximab therapy on FFM may be also influenced by improved physical activity and dietary intake. Another possible limitation of the comparative study is the high percentage of disease in a remission status in the group on conventional treatment. Despite the above reported limitations we are confident that there were no major selection bias since no significant differences in the basic characteristics between excluded and enrolled patients were found. Even if our results come from a relatively small group of patients, it appears that a short course of infliximab therapy improves nutritional parameters in adult CD patients. In agreement with our findings, in previous studies, carried out mainly on pediatric population and focusing on the measurement of fat free mass, both by means of BIA or DEXA, an increased FFM following infliximab treatment had been shown [22,23].

In conclusion, findings of our study show that CD patients in clinical remission on conventional therapy are characterized by a significantly lower lean body mass and mean phase angle score compared to those on infliximab therapy. In patients with active disease, following the induction protocol with infliximab, the fat free mass increased, although not significantly, and the mean phase angle score normalized. Long term studies using larger sample sizes would provide stronger evidence of the role of biological therapy on fat free mass and BIA-derived phase angle in CD patients and better validate the diagnostic accuracy of phase angle as a nutritional indicator in IBD patients.

Conflict of interest
None declared.

Acknowledgments and Disclosures

The authors have nothing to disclose.

References

[1] Mijac DD, Janković GL, Jorga J, et al. Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. European Journal of Internal Medicine 2010;21:315–9.
[2] Gassull MA. Nutrition and inflammatory bowel disease: its relation to pathophysiology, outcome and therapy. Digestive Diseases 2003;21:220–7.
[3] Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2003;17:307–20.
[4] Capristo E, Addolorato G, Mingrone G, et al. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. The American Journal of Gastroenterology 1998;93:2411–9.
[5] Alastair F, Emma G, Emma P. Nutrition in inflammatory bowel disease. JPEN. Journal of Parenteral and Enteral Nutrition 2011;35:571–80.
[6] Bryant R, Trott, Bartholomeusz F, et al. Systematic review: body composition in adults with inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2013;38:213–25.
[7] Lukaski HC, Johnson PE, Bolonchuk WW, et al. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. The American Journal of Clinical Nutrition 1985;41:810–7.
[8] Norman K, Stobaus N, Pirlich M, et al. Bioelectrical phase angle and impedance vector analysis—clinical relevance and applicability of impedance parameters. Clinical Nutrition 2012;31:854–61.
[9] Norman K, Kirchner H, Lochs H, et al. Malnutrition affects quality of life in gastroenterology patients. World Journal of Gastroenterology 2006;12:3380–5.
[10] Gupta D, Lis CG, Dahlk SL, et al. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. The British Journal of Nutrition 2004;92:957–62.
[11] Werkstetter KJ, Ullrich J, Schatz SB, et al. Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. Journal of Crohn's and Colitis 2012;6:665–73.
[12] Targan SR, Hanauer SB, van Deventer SJ, et al. A short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn disease cA2 Study Group. The New England Journal of Medicine 1997;337:1029–35.
[13] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. Lancet 2002;359:1541–9.
[14] Travis S, Van Assche G, Dignass A, et al. On the second ECCO Consensus on Crohn's disease. Journal of Crohn's and Colitis 2010;4:1–6.
[15] Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–44.
[16] World Health Organization (WHO). Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organization Technical Report Series 1995;854:1–452.
[17] Thayu M, Denson LA, Shults J, et al. Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease. Gastroenterology 2010;139:430–8.
[18] Vespasiani Gentilucci U, Caviglia R, Picardi A, et al. Infliximab reverses growth hormone resistance associated with inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2005;21:1063–71.
[19] Merola E, Mattioli E, Minimo C, et al. Immunohistochemical evaluation of pRb2/p130, VEGF, EZH2, p53, p16, p21 waf-1, p27, and PCNA in Barrett's esophagus. Journal of Cellular Physiology 2006;207:512–9.
[20] Valentini L, Schaper L, Buning C, et al. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition 2008;24:694–702.
[21] Lochs H, Dejong C, Hammarqvist F, et al. ESPEN guidelines on enteral nutrition: gastroenterology. Clinical Nutrition 2006;25:260–74.
[22] Wiese D, Lashner B, Seidner D. Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. Nutrition in Clinical Practice 2008;23:551–6.
[23] Nakahigashi M, Yamamoto T. Increases in body mass index during infliximab therapy in patients with Crohn's disease: an open label prospective study. Cytochine 2011;56:531–5.