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The Effect of anti-TNFα Induction Therapy on the Nutritional Status and Dietary Intake in Inflammatory Bowel Disease

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ABSTRACT

Background & Aims: Patients suffering from inflammatory bowel disease (IBD) are at a high risk of malnutrition and retain an altered body composition. We hypothesized that anti-tumor necrosis factor (anti-TNF) alpha therapy may improve dietary intake and have a beneficial influence on body composition in these patients.

Methods: Our study involved 40 IBD outpatients (33 Crohn's disease, 7 ulcerative colitis); 24 of these received adalimumab (160/80/40EOW) and 16 were treated with infliximab (5 mg/kg at week 0, 2, 6, and subsequently every 8 weeks). Body composition was measured with bioelectrical impedance analysis, while dietary intake was recorded prior to initiating biologicals and 3 months afterwards. Body composition indexes: fat-free mass index [FFMI], body fat mass index [BFMI]) were calculated in kg/m^2.

Results: Baseline BMI (kg/m^2) and muscle parameters increased significantly at the end of the observational period (BMI: 23.81±7.19 vs. 24.52±7.34, p<0.001; FFMI: 17.64±3.00 vs. 18.14±3.08, p<0.001; at week 0 vs. 12, respectively). However, no significant changes were detected in the fat parameters (BFMI: 6.21±5.20 vs. 6.44±5.27, respectively). We found no significant difference between the effects of adalimumab vs. infliximab on body composition (deltaFFMI: 0.55±0.82 vs. 0.43±0.69; deltaBFMI: 0.23±0.85 vs. 0.21±1.01, respectively). No significant difference was observed in the extent of changes in parameters whether the patients were on corticosteroids (n=15) or not (n=25) at week 0 (deltaFFMI: 0.44±0.84 vs 0.59±0.72; deltaBFMI: 0.36±1.12 vs. 0.09±0.71, respectively).

Conclusion: Our findings suggest that muscle parameters improved during the anti-TNF induction therapy, while fat parameters did not change significantly. Thus, induction anti-TNF therapy might have a beneficial effect on body composition.

Key words: TNF-alpha – body composition – malnutrition – inflammatory bowel diseases – nutritional status.

Abbreviations. ADA: adalimumab; BCM: body cell mass; BFM: body fat mass; BFMI: body fat mass index; BIA: bioelectrical impedance analysis; BMI: body mass index; CD: Crohn's disease; ECW: extracellular water; FFM: fat-free mass; FFMI: fat-free mass index; IBD: inflammatory bowel disease; ICW: intracellular water; IFX: infliximab; NF-κB: nuclear factor kappa-B; PDAI: perianal disease activity index; RA: rheumatoid arthritis; SMI: skeletal muscle mass index; SMM: skeletal muscle mass; TBW: total body water; TNF-alpha: tumor necrosis factor alpha; UC: ulcerative colitis

INTRODUCTION

Inflammatory bowel diseases (IBD) are systemic autoimmune diseases causing chronic inflammation in the digestive tract. Although the etiology of the diseases is still uncertain, our knowledge of the molecular mediators and the mechanisms of chronic inflammation has expanded.

The most widely studied cytokine in IBD is the tumor necrosis factor alpha (TNF-α), which also has a crucial role in the regulation of nutritional homeostasis. TNF-α is a homotrimeric protein that exists in both transmembrane and soluble forms. It activates and enhances the migration of leukocytes, amplifies the production of other pro-inflammatory cytokines, such as IL-1, IL-6 and IL-8, as well as stimulating nuclear transcription factors to induce and maintain the inflammatory response [1]. In addition to its contribution to the immune response, TNF-α influences nutrition homeostasis by inhibiting IGF-1 induced anabolism [2] through increasing lipolysis and stimulating proteolysis and muscle catabolism via a nuclear factor (NF)-κB-dependent process [3, 4]. These mechanisms may lead to weight and muscle loss and also to an altered body composition. Hence, TNF-α is also known as "cachectin." Compared to healthy controls, Crohn's disease (CD) patients exhibit an increased

TNF-α level in the involved areas of the bowel wall [5], blood, and stools [6]. The blockage of the TNF-α pathway is a noteworthy target in the treatment of IBD. TNF-α inhibitors, such as murine-human chimeric infliximab (IFX) and fully human adalimumab (ADA) have demonstrated efficacy in both CD and ulcerative colitis (UC) patients [7].

Apart from administering the appropriate treatment, monitoring nutritional status is a particularly relevant part of IBD patient care, as these patients are at a high risk of malnutrition. The symptoms of acute disease (such as diarrhoea, reduced nutrition absorption, inadequate dietary intake, insufficient physical exercise, decreased appetite), as well as chronic inflammation (due to a release of pro-inflammatory cytokines), may lead to altered body composition, muscle loss and moreover, sarcopenia [8, 9]. Sarcopenia can be considered 'primary' (or age-related) when no other cause is evident but ageing itself; it can be considered 'secondary' when one or more other causes are evident [10]. Among IBD patients, the secondary sarcopenia is of major interest since the majority of the patients are young adults. Nutritional status and particularly the presence of chronic disorder-related secondary sarcopenia may worsen the disease outcome in chronic disorders and impair the quality of life among IBD patients [11-14]. As TNF-α is an activator of NF-κB, it has a remarkable effect on metabolic pathways. Its inhibitors prevent the activation of NF-κB [15]; therefore they might influence the nutritional status and body composition as well.

We hypothesized that the TNF-α pathway blockade affects the nutritional status of the patients. Furthermore, our assumption was that due to the TNF-α therapy and dietary intake, the nutritional status of the patients may improve and their body composition may change favorably.

Thus, we aimed to assess the changes in body composition during the initiation phase of anti-TNF-α therapy in IBD patients. We measured body composition with bioelectrical impedance analysis (BIA) and recorded dietary intake before initiating biologicals and three months thereafter.

MATERIAL AND METHODS

Patients

We included 40 IBD outpatients who had initiated anti-TNF-α therapy (33 CD and 7 UC patients) in our prospective cohort study. The inclusion period was October 2013 to February 2014. The diagnosis of IBD was based on the Lennard-Jones criteria [16], while UC and CD were classified into subgroups based on the Montreal classification [17].

Indications of anti-TNF-α therapy were according to international guidelines [18, 19] and the administration criteria of the National Health Insurance Fund of Hungary were taken into consideration as well. The indications of anti-TNF alpha therapy were steroid dependency (defined by being unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months since starting steroids, without a recurrent active disease, or having a relapse within 3 months after stopping steroids) [20] and/or having a moderate-severe disease that is non-respondent to the conventional anti-inflammatory therapy. Altogether, 24 patients received adalimumab (ADA, 160 mg at week 0, 80 mg at week 2, then 40 mg every other week) and 16 patients were treated with IFX (5 mg/kg at week 0, 2, 6 and subsequently every 8 weeks) during the study period. Activity of UC, confirmed by endoscopy as an endoscopic Mayo score equal to 2 or more was the inclusion criterion. Concerning UC, the clinical severity of the disease was assessed by the partial Mayo score (pMayo)[21] and it was considered to be mild under pMayo of 2, moderate from 3 to 5 and severe over 6. Crohn's disease activity was determined by using the CD activity index (CDAI) and the perianal disease activity index (PDAI). Patients were considered to have a mild disease in the case of a CDAI 150-250 or PDAI 3-5; moderate with CDAI between 250-450 or PDAI 6-9, and severe with CDAI >450 or PDAI >9 [20]. Further disease specific information and physical characteristics were gathered from the patients and their files during their visit to our outpatient department.

Exclusion criteria were previous anti-TNF-α or other cytokine therapy in the preceding 12 months, hypersensitivity to IFX in IFX treated patients, associated endocrine or chronic disorders (e.g. diabetes mellitus), and known active malignancy or pregnancy. We also excluded patients with proved fibrotic stenosis, due to the local financial regulation and the fear of a high drop-off rate.

The bioelectrical impedance analysis (BIA) measurement was contraindicated with implanted defibrillation or a cardiac pacemaker. To avoid the inaccuracy of the BIA measurements, patients with clinically manifest water imbalance (e.g. persistent limb oedema or notable ascites) were also excluded.

Concomitant medications (5-amino salicylic acid [5-ASA] preparations and immunomodulatory drugs) were kept as stable as possible for 12 weeks prior to introducing biological therapy. Steroid dependent patients with a stable steroid dose in the preceding 12 weeks were included, while any change in the steroid dose within the same timeframe was considered an exclusion criterion.

The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics and was performed in accordance with the Helsinki declaration. All participants provided written informed consent to participate in the study.

Body composition analysis

Body composition analysis was conducted with BIA, employing the InBody 720 body analyzer. The measurement was performed right before initiating biological therapy, and was repeated 3 months later. Patients were measured fasting, subsequent to urination and undressed to underwear. All jewelry and watches were removed prior to measurement. All BIA measurements were performed by the same trained personnel and on the same equipment to minimize the inter-measurement errors.

The InBody 720 device uses an electrical current at 5, 50, 250, 500 and 1000 kHz to measure the complex impedance of the five body segments (four limbs and the trunk) separately [22]. During the process, body composition parameters were automatically recorded [23], i.e. body weight, body mass index (BMI), body fat mass (BFM), fat free mass (FFM), skeletal muscle mass (SMM), skeletal lean mass (SLM), total body water (TBW), extracellular and intracellular fluid

(ECW, ICW), and body cell mass (BCM). We calculated body composition indexes from the computed values (fat-free mass index [FFMI], skeletal muscle index [SMI] and body fat mass index [BFMI]) [24], allowing for the interpretation of body composition variables, regardless of height. Based on recent recommendations, sarcopenia risk was determined if the FFMI was below 17.0 kg/m^2 for males and 15.0 kg/m^2 for females, or if the SMI was below 8.87 kg/m^2 for males and 6.42 kg/m^2 for females [25].

Nutritional assessment

Dietary assessment was conducted by utilizing recording sheets [26]. All nutrients that the participants consumed for two days (one weekday and one weekend day) before commencing anti-TNF therapy and for three days (two weekdays and one weekend day) at week 12 were recorded. A skilled clinical dietician interviewed the patients to clarify the recorded data. Currently, there are no standards about the number of days that the dieticians need for calculating an average. Based on several of our cases we found that before the anti-TNF therapy the patients' diets were almost the same every day, as they could eat only few foods because they felt that most foods caused pain. But after 12 weeks the patients said they could consume a larger quantity and more kind of foods because their pain had diminished. The difference was represented in our pre-calculations too, since the standard deviation (SD) of the different nutrients was higher at week 12 when we calculated with one weekday and one weekend day (energy: 1834.7 + 468.8 kcal, protein: 87.5 + 37.4 kcal). We realized that this time more days would be better to calculate, because more kind of foods could be consumed, and the calculated energy was more different day per day, so we decided to evaluate for 3 days in order to represent better the average daily intake. There was no significant difference if we calculated with the average of one or two weekdays, so our final observations did not change. The average nutrient intake was calculated with Nutricomp DietCad® software, especially developed for dietetics, and verified in the Hungarian patient population [27]. The program automatically calculates the energy content (in kcal and kJ), the main nutrients (protein, carbohydrate, fat, fiber intake in grams), minerals, trace elements and the vitamin amount of the consumed food. The main nutrient intake was calculated and employed in analyses regarding body weight (g/kg).

Statistical analysis

Data analysis was performed on the total study (total group) and on subgroup populations based on the agent of anti-TNF-alpha therapy, disease type and baseline disease activity. Distribution of the examined data was checked by Kolmogorov-Smirnov and Shapiro-Wilk test. For independent samples with normal distribution, Student's *t*-test, one-way analysis of variance (ANOVA) and post hoc test (Sheffe) were applied. For dependent samples, paired *t*-test was applied, in case of normal distribution. For non-normal distributed dependent variables Wilcoxon signed rank test was applied. Associations between categorical variables were assessed by chi-square and Fisher's exact tests. For the matched-paired dependent data marginal homogeneity test, the Stewart-Maxwell test was used. Results are presented as mean± SD. To identify the correlation between nutrient intake and the change in body composition parameters, Pearson's correlation was applied. For correlation, the applied threshold was $r > 0.7$ (strong correlation). Level of significance was considered $p < 0.05$. For statistical calculations SPSS 22.0 and STATISTICA 13 and software were used. For marginal homogeneity test MH Program 1.2 was used.

RESULTS

Overall, 40 IBD patients were included in the study: 33 (82.5%) of them had CD, while 7 (17.5%) had UC; their mean age was 33.4±12.9 years. The ratio male:female was 6:4 (24 males, 16 females). The main characteristics of our cohort are displayed in Table I.

During the 12-week study period, no participants quitted the study because of a failure to respond to the biologicals. Moreover, we observed that distribution of the week 0 severity grade differed significantly from the distribution of the week 12 severity grade in the same subjects when the marginal homogeneity was tested (Stuart-Maxwell chi-squared=15.2, df=2, $p < 0.001$). The distribution of the disease activity is presented in Fig. 1. Regarding concomitant therapy, 67.5% (n=27) of the participants received 5-ASA, 45.0% (n=18) received azathioprine, and 37.5% (n=15) of the patients used corticosteroids at the time when biologicals were introduced. The mean duration of the actual corticosteroid therapy was 105 days.

According to our findings, baseline BMI and muscle parameters increased significantly during the observed period, while no significant changes were detected in the main body fat parameters. Anthropometric parameters and body composition features, both at baseline and at week 12, are presented in Table II. A significant improvement was observed in the muscle parameters among male patients when analyzing changes of body composition parameters for the two genders, but these changes were not significant in women (Fig. 2). When starting biological therapy, 30% (n=12) of the patients were at risk of sarcopenia with regard to FFMI and 12.5% (n=5) with regard to SMI. By the end of the induction therapy, the proportion of those being at risk decreased to 25% (n=10) and 5% (n=2), respectively (Fig. 3).

Patients were divided into subgroups based on the type of anti-TNF-α agent, type of disease and baseline disease activity. When patients were categorized according to the disease type, we found a significantly greater change regarding muscle parameters in CD than in UC patients (Table III). However, in order to draw firm conclusions with biological significance, the number of patients in each subgroup must be higher. As for the impact of the different anti-TNF-α therapies on body composition, we found no significant difference between the effects of ADA vs. IFX treatment (see Table III for relevant data). A significant difference was observed in the change of muscle parameters regarding baseline disease activity. The less severe disease group demonstrated a greater improvement in FFMI, SMI and SLMI, while fat parameters did not show any significant change (Table IV).

Table I. Baseline demographical and clinical characteristics of studied patients

Age		33.4± 12.9 years	
Gender (female, %)		16 (40%)	
Mean disease duration		93.5 months	
Concomitant medication		5-ASA	1987.6 ± 1665.9mg
		Azathioprine	150 ± 72.76mg (2.30 ± 0.98mg/kg)
		Steroid	28.42 ± 20.09mg (0.42 ± 0.32mg/kg)
Crohn's Disease, n (%)	Disease type	Inflammatory (B1)	19 (57.6%)
		Penetrating (B3)	14 (42.4%)
		Stricturing (B2)	0 (0.0%)
	Location	Small bowel involvement# (L1+L3)	24 (72.7%)
		Colon Involvement (L2)	9 (27.3%)
	CDAI	Baseline	270.5±98.7
		Week 12	96.7±80.9
Ulcerative Colitis, n (%)	Location	Left sided (E1+E2)	1 (14.3 %)
		Pancolitis (E3)	6 (85.7%)
	pMayo	Baseline	7.3 ± 0.8
		Week 12	2.3 ± 2.4

CDAI: Crohn's Disease Activity Index, pMayo: partial Mayo score. Disease location and Crohn's disease types were based on Montreal classification. #None of the included CD patients had extensive small bowel involvement. Values are presented as % or as means ± SD.

Taking into account the previously used medication, there was no significant difference in the extent of changes in body composition parameters, whether the patients were on corticosteroids (n=15) or not (n=25) at week 0 (deltaFFMI: 0.44±0.84 vs 0.59±0.72, p=0.58; deltaSMI: 0.17±0.48 vs 0.31±0.47, p=0.41; deltaBFMI: 0.366±1.12 vs. 0.09±0.71, p=0.68 on and without steroids, respectively). As for azathioprine usage, there was no statistically significant difference in the change of body composition either (deltaFFMI: 0.68±0.91 vs. 0.35±0.31, p=0.18; deltaSMI: 0.26±0.69 vs. 0.20±0.38, p=0.62; deltaBFMI: 0.26±0.69 vs. 0.20±1.06, p=0.86 on and without azathioprine, respectively).

We observed significant differences in inflammatory laboratory parameters from week 0 (C-reactive protein 23.9 g/L) to week 16 (13.4 g/L, p=0.01). There was no significant difference between the baseline hemoglobin level (130.0 g/L) and that of week 16 (127.5 g/L, p=0.33). The serum albumin concentration also remained unchanged throughout the study (41.5 g/L vs. 41.7 g/L, p=0.83). Furthermore, there was no significant difference in either the serum cholesterol (4.5 mmol/L vs. 4.3 mmol/L, p=0.14) or the triglyceride levels (1.27 mmol/L vs. 1.28 mmol/L, p=0.96).

Upon evaluation of the dietary intake, we found that both the energy intake and the amount of main nutrient (protein, carbohydrate, fat) consumption improved significantly. However, the proportion of the mean nutrient intake did not change significantly during the observed period (Table V).

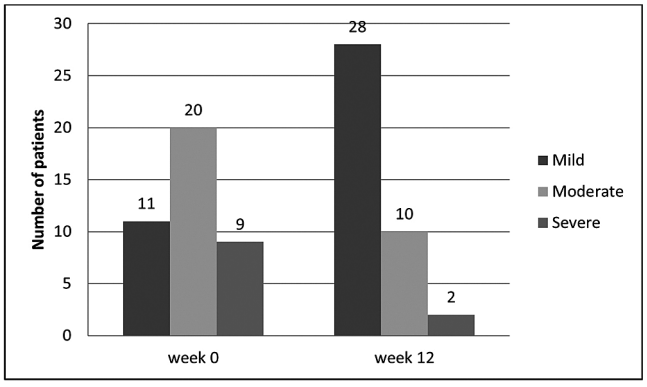

Fig. 1. Changes in disease activity during the examined period.

Table II. Changes in the main body composition parameters

	Baseline	Week 12	P value
Weight (kg)	63.40 (58.82-79.40)	63.70 (58.49-82.65)	<0.001*
BMI (kg/m^2)	21.75 (19.20-26.55)	22.50 (20.17-27.02)	<0.001*
FFMI (kg/m^2)	17.64±3.00	18.14±3.08	<0.001*
SMI (kg/m^2)	9.81±1.83	10.05±1.90	0.003*
BFMI (kg/m^2)	4.57 (2.74-7.78)	4.76 (2.94-8.65)	0.120
Percent of body fat (%)	20.85 (15.23-32.15)	20.20 (14.75-31.10)	0.532
Visceral fat area (cm^2)	95.65 (58.40-136.75)	85.00 (57.37-142.02)	0.730
Body cell mass (kg)	32.65 (27.30-41.45)	33.95(28.57-42.22)	<0.001*

BMI: body mass index; FFMI: fat-free mass index; SMI: skeletal muscle mass index; BFMI: body fat mass index.
Normally distributed values are presented as means± SD, non-normal distributed data are presented as median (quartile 1 – quartile 3). * reflects the significance of the differences within groups between baseline and week 12.

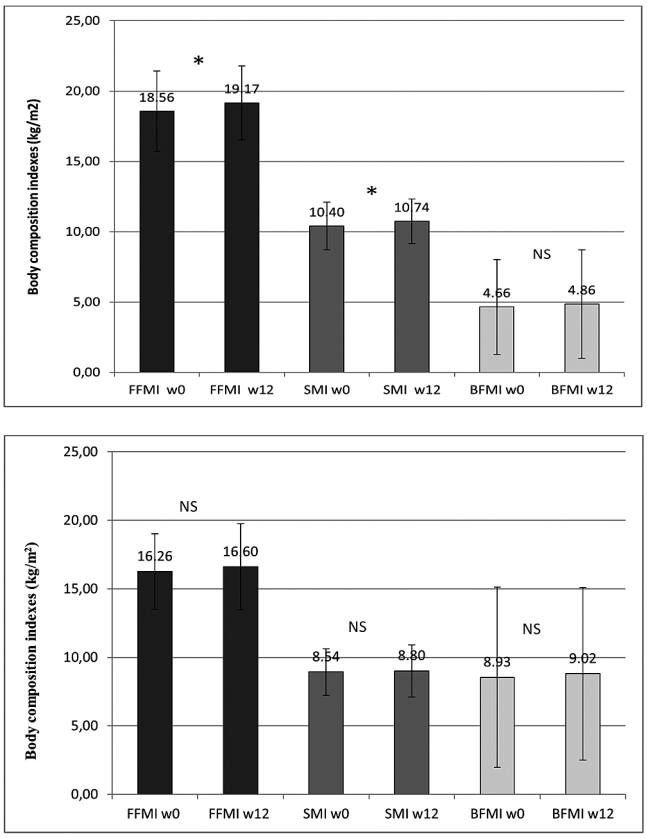

Fig. 2. Changes of body composition parameters during induction therapy in males (A) and females (B). FFMI: fat-free mass index, SMI: skeletal muscle mass index. * statistically significant results. NS: non-significant.

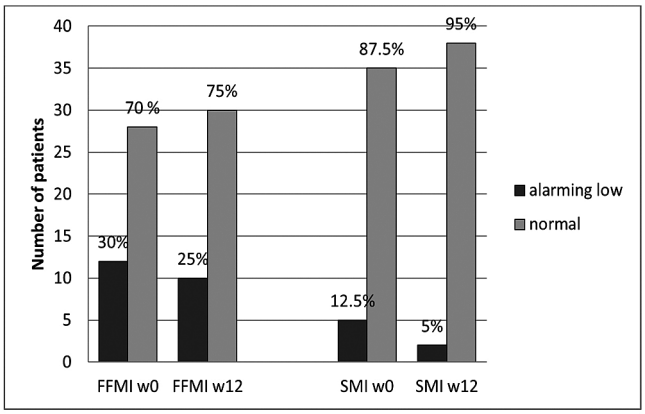

Fig. 3. The change in the ratio of patients at risk during induction therapy. FFMI: fat-free mass index, SMI: skeletal muscle mass index.

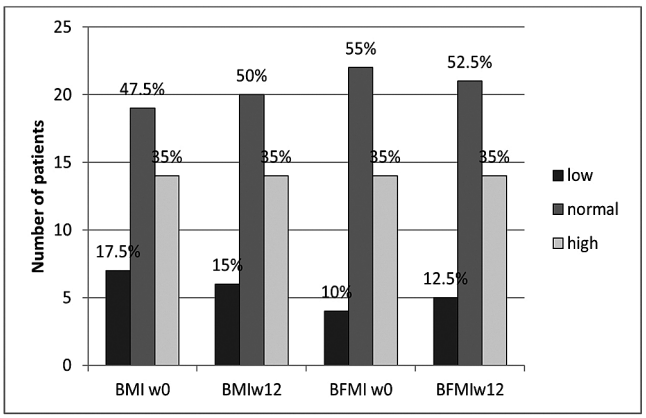

Fig. 4. Ratio of patients with altered BMI and BFMI. BMI: body mass index, BFMI: body fat mass index.

No strong correlation was observed between the increased intake of protein and the muscle body composition parameters (deltaFFMI vs. delta protein intake, r=0.145; p=0.406, deltaSMI vs delta protein intake: r=0.195. p=0.261).

DISCUSSION

The importance of the nutritional status, and body composition in particular has received increased attention in the past few decades. Previously employed nutritional status assessments, which were mainly based on body weight, seem to be obsolete, due to the fact that they do not provide sufficient information concerning the body composition. Recently, skeletal muscle and adipose tissue have been given an important role in the maintenance of metabolic homeostasis, as they were detected to be cytokine-producing organs [28, 29]. Loss of muscle mass, indicated by decreased FFM and SMM, may lead to the development of sarcopenia, which may worsen

Table III. Changes of body composition according to disease type and anti-TNF therapy

	UC	CD	ADA	IFX
delta Weight (kg)	0.8±2.7	2.4±3.0	2.4±3.2	1.7±2.7
delta BMI (kg/m²)	0.29±0.88	0.80±1.01	0.79±1.08	0.59±0.89
delta FFMI (kg/m²)	-0,04±0.69*	0.61±0.74*	0.55±0.82	0.43±0.69
delta SMI (kg/m²)	-0.24±0.33**	0.34±0.44**	0.32±0.50	0.11±0.42
delta BFMI (kg/m²)	0.56±1.20	0.16±0.83	0.23±0.85	0.21±1.01
delta Percent of Body Fat (%)	1.8±3.7	0.0±3.1	0.3±2.8	0.4±3.9
delta Visceral Fat Area (cm²)	15.6±72.5	-5.6±20.0	-5.0±18.0	2.7±51.0

UC: ulcerative colitis, CD: Crohn's Disease, ADA: adalimumab, IFX: infliximab, BMI: body mass index, FFMI: fat-free mass index, SMI: skeletal muscle mass index, BFMI: body fat mass index. Delta reflects week 0 parameter subtracted from week 12 parameter
All values are presented means ± SD. * reflects the comparison of the differences within FFMI of UC and CD patients (p=0.038). ** reflects the comparison of the differences within SMI of UC and CD patients (p=0.002)

Table IV. Changes of body composition parameters according to disease severity

	mild	moderate	severe
delta Weight	3.54±3.59	1.87±2.60	0.98±2.67
delta BMI	1.16±1.19	0.63±0.88	0.34±0.91
delta FFMI	1.02±0.74*	0.46±0.68	-0.05±0.61*
delta SMI	0.52±0.42**	0.28±0.44 ◊	-0.19±0.31**, ◊
delta BFMI	0.12±0.95	0.13±0.70	0.59±1.22
delta Percent of Body Fat (%)	-0.77±3.53	0.25±2.59	1.82±3.82
delta Visceral Fat Area	-7.35±20.59	5.80±20.06	13.38±63.58

BMI: body mass index,; FFMI: fat-free mass index; SMI: skeletal muscle mass index; BFMI: body fat mass index. Delta reflects week 0 parameter subtracted from week 12 parameter.
All values are presented means± SD. * differences within mild and severe disease activity subgroups (p=0.005). ** differences within mild and severe disease activity subgroups (p=0.002). ◊: reflects the comparison of the differences within moderate and severe disease activity subgroups (p=0.023).

disease outcome in chronic disorders, as well as raise the risk of infections and drug toxicity. Simultaneously, increased adipose mass may increase the risk of cardiovascular co-morbidities and the development of type 2 diabetes mellitus.

Previous studies revealed contradictory results concerning the effects of anti-TNF-α therapy on body composition. Serelis et al. investigated the effects of anti-TNF-α treatment in 19 women suffering from rheumatoid arthritis (RA). During a one-year follow-up, the authors found that although anti-TNF therapy did not have any significant effect on body composition, it increased serum adiponectin levels [30]. Conversely, during a follow-up of 21 months, Engvall et al. observed that body fat mass increased significantly among the involved 40 RA patients receiving IFX therapy. This effect was not achieved with the combination of other disease modifying drugs, despite a similar reduction in disease activity [31]. Di Renzo et al. examined 40 patients suffering from psoriasis and psoriatic arthritis for 24 weeks, and demonstrated that a blockage of TNF-α bioactivity is related to fat and lean mass increase [32].

Even though monitoring the nutritional status is a relevant part of IBD patient care, the effect of the different treatments on body composition still lacks adequate attention. Wiese et al. followed 7 CD patients during a 6-month IFX therapy and found improvement in both inflammation and nutrition indexes. The study was unclear about whether weight gain was due to an increase in fat or in lean muscle mass [33]. Bultman et al. followed 199 CD patients receiving ADA for 3 months and observed that apart from a secondary non-response to IFX, a higher BMI was predictive for a dose escalation during ADA treatment. However, the effect of body composition was not examined [34]. In a recently published study of Subramaniam et al., the changes in the muscle volume were examined with MRI during the first 25 weeks of IFX, yielding results of significant muscle gain [35]. Their findings were similar to ours: a greater muscle improvement was detected in males, regardless of the steroid intake. However, the dietary intake was kept stable in the Subramaniam et al. study, contrary to ours, where food intake increased significantly.

To the best of our knowledge, the present study is the first to evaluate body composition in IBD patients under treatment with different anti-TNF-α agents. We detected a significant improvement in the nutritional status of IBD patients during the induction phase of the anti-TNF-α therapy. According to our findings, baseline BMI increased significantly and the risk of sarcopenia based on FFMI decreased (from 30% to 25%). Moreover, our hypothesis seems to be valid, as body composition was observed to change favorably during the follow-up period: body composition indexes indicate

Table V. Dietary intake results

Daily nutrient intake		Baseline	Week 12	p
Energy	Total energy intake (kcal)	1333.3±399.3	1817.0±487.0	<0.001*
	Intake per weight (kcal/kg)	17.19 (13.73-25.98)	25.05 (20.17-33.19)	<0.001*
Protein	Total protein intake (g)	59.67 (45.78-70.54)	83.09 (61.17-98.91)	<0.001*
	Protein intake per weight (g/kg)	0.92 (0.56-1.29)	1.13 (0.81-1.50)	<0.001*
	Protein intake En %	17.75 (15.76-19.90)	17.38 (15.72-19.72)	0.633
Carbo-hydrate	Total carbohydrate intake (g)	168.6±53.3	216.4±62.1	<0.001*
	Sugar intake (g)	17.25 (10.72-21.99)	28.82 (16.96-38.36)	<0.001*
	Carbohydrate intake per weight (g/kg)	2.5±1.0	3.2±1.2	<0.001*
	Carbohydrate intake En %	50.3±8.2	47.3±6.6	0.051
Fat	Fat intake(g)	45.6±18.4	67.2±21.1	<0.001*
	Fat intake per kg (g/kg)	0.57 (0.40-0.96)	0.98 (0.72-1.14)	<0.001*
	Fat intake En %	30.1±7.6	32.9±6.6	0.081
Dietary fibre	Dietary fibre (g)	11.73 (9.72-15.44)	15.29 (12.78-18.87)	0.004*

Normal distributed values are presented means± SD, non-normal distributed data are presented median (quartile 1 – quartile 3).* Reflects the significance of the differences within groups between baseline and week 24.
Guide for estimating nutritional requirement in stable patients: Energy: 20-35 kcal/kg/day (in clinical practice 25-30 kcal/kg/day for the majority of the patients). Protein: 0.8-2.0 g/kg/day (in clinical practice 0.8-1.0 g/kg/day for the majority of patients, in those who are metabolically stressed, requirements may be higher). Fat: 1 g/kg/day for the majority of the patients. Carbohydrate: 4-5 g/kg/day for the majority of the patients. The distribution of energy intake is: 12-15% protein, 30-35% fat, 50-55% carbohydrate for the majority of patients [36, 37].

an increased muscle content, but fat parameters did not change significantly. The aforementioned changes were more pronounced in male than in female patients. The parameters characterizing muscle mass improved in all IBD patients. The clinical relevance of the subgroup analysis is questionable due to the relatively low number of UC patients.

Concerning the pharmacological treatment, the anti-TNF-α agents analyzed seem to have the same effect on body composition. Approximately one third of the patients had been receiving corticosteroids when biological therapy was introduced. Corticosteroids influence muscle and adipose metabolism in several ways; hence the question arises how they affect the evolution of body composition. Body composition parameters exhibited no significant change, whether the patients were on corticosteroids at week 0 or not.

We analyzed changes in the dietary intake of the patients in order to explore the possible underlying causes of our findings and discovered that both the energy intake and the consumption of main nutrients increased. While baseline energy, fat and carbohydrate intake was lower than among average healthy adults, it approached the recommended amount following the induction phase. Fortunately, it seems that the protein intake of patients was relatively high originally, and it increased even further. However, the energy proportion of the protein, fat and carbohydrate intake did not change significantly. Thus, the quantity of food intake improved, while the quality of food consumption did not vary. These findings highlight the importance and necessity of individualized dietary counseling.

Our results can be explained by several speculative reasons: TNF-α inhibition itself improves the nutritional status by blocking the lipolytic and proteolytic effect of the inflammatory cytokine. In addition, due to its mucosal healing effect, the biological treatment improves nutrient absorption and utilization. On the other hand, as disease activity decreases, the physical activity and appetite of patients may improve, and this may increase food intake, physical endurance and capacity. We surmise that the detected changes are a result of the aforementioned processes acting collectively.

We acknowledge some limitations of our study. The relatively low number of cases for the subgroup analyses, as well as the short follow-up period and heterogeneous patient population may limit the general implications of the study. We must admit that the BIA method itself has limitations, too; for example, it may not be accurate in dehydration or over-hydration. To minimalize the inaccuracy, all BIA measurements were performed in standardized circumstances. All in all, BIA is an easy-to-use reproducible, relatively inexpensive method and contrary to other measurements (e.g. CT or DEXA examination) it does not use ionizing radiation. In subjects being in their reproducible age, as most of the IBD patients are, a method without ionizing radiation should be the first choice in our opinion. Furthermore, our study design did not allow for an evaluation of the changes in functional muscle parameters and physical activity during the examined period. Determining the precise mechanisms of muscle parameter improvement requires further evaluation regarding the modified cytokine profile of nutrition homeostasis, the effects of mucosal healing on protein-losing enteropathy, as well as the appetite and the dietary intake of proteins. To achieve far-reaching clinical implications would necessitate a larger number of participants, a longer follow-up time and an extension to other methods (e.g. hand grip).

CONCLUSIONS

Comparing baseline and week 12 data, we observed a significant improvement in BMI and in body composition muscle parameters. The risk of sarcopenia, as defined by FFMI and SMI, decreased during the anti-TNF induction therapy, while fat parameters did not change significantly. Our findings suggest that the induction of anti-TNF therapy has a beneficial effect on the nutritional status and body composition regardless of maintaining or not the steroid therapy. We observed no difference between IFX and ADA treatment in their effect on body composition.

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Authors' contribution: A.A.C., A.M. and M.P. participated in the design of the study, performed the measurements and the statistical analysis. A.A.C. wrote the manuscript. Z.P. and K.B. helped in data collection and the interpretation of data. A.M., S.D. and E.P. recorded dietary log sheets and analyzed the data. All authors read and approved the manuscript.

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