# The importance of nutritional status in inflammatory bowel disease

Ph.D. Thesis

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## 1. Introduction

Malnutrition is defined as an abnormal nutritional state caused by the lack or altered ratio of one or more nutrients. Inflammatory bowel disease (IBD) patients are at high risk of being malnourished due to the nature of the disease.

The recently published guideline of the European Society for Clinical Nutrition and Metabolism (ESPEN) also highlights the importance of malnutrition screening, however, there is still no clear recommended method for assessing nutritional status.

Body weight and body mass index (BMI) based methods can be an important first step in screening, but BMI does not provide enough information about the body composition. Abnormal changes in the body composition, including reduced fat-free mass, may potentially result in a worse outcome for chronic diseases and a reduced quality of life.

Body composition can be determined by several methods. Bioimpedance-based body composition analysis (BIA) is an easy-to-use, cheap, reproducible test that does not use

ionizing radiation. This is a very important aspect for IBD patients, since they are mostly of reproductive age.

Nowadays, potential prognostic factors of IBD and treatment efficacy receive more attention, especially in connection with biological treatment. Currently, two TNF-α inhibitors are used in IBD: infliximab (IFX), and adalimumab (ADA). ADA (contrary to IFX), is currently added in standard dose, independently of body weight. According to data, BMI can affect ADA's long-term efficacy.

## 2. Objectives

We aimed to evaluate the general nutritional status and malnutrition risk of IBD outpatients. We investigated whether individual body composition parameters influence the course and prognosis of the disease. We also aimed to investigate the effect of anti-TNF-α therapy on body composition and bone metabolism among IBD patients.

As IBD patient care is becoming more and more personalized, we aimed to assess whether ADA treatment

should be dosed on the basis of body composition. We hypothesized that individual body composition parameters may influence the stability of the serum level of the biological agent.

## 3. Methods

To anwer these questions, we performed the following studies:

**A:** We assessed the risk of malnutrition by a questionnaire method called Malnutrition Universal Screening Tool (MUST) and we performed body composition analysis by BIA device.

**B:** We aimed to assess whether pathological nutritional status may be a prognostic factor of IBD outcome. We subsequently followed our outpatients for three years. The incidence of adverse events (acut flares, need for hospitalization, number of days spent in hospital, the need for surgery due to inflammatory bowel disease, the presence of complications, duration until the first operation and mortality) was compared with the baseline body composition parameters.

**C:** We aimed to assess the effect of anti-TNF-α on the body composition and bone metabolism. At the beginning of the study, BIA body composition analysis and bone density analysis based on DEXA were performed and relevant bone metabolism laboratory tests were performed. Body composition analyses were repeated at week 12, then at months 6 and 12, respectively.

**D:** The stability of ADA serum levels and the relationship between body composition were examined during subcutaneous administration of standard doses ADA. Baseline BIA-based body composition analysis was performed. ADA trough levels and antibody titers were determined by ELISA prior to the next drug administration at weeks 6 and 12, respectively.

### 3.1. Patients

IBD outpatients, at the 2nd Department of Internal Medicine, Semmelweis University were enrolled to the study. The inclusion period lasted from October 2013 until February 2014. The main exclusion criteria were: known endocrine or metabolic disorders, pregnancy, chronic co-

morbidity, cancer or permanent tube or parenteral nutriton therapy. In addition, patients with <16 kg/m$^2$ or > 34 kg/m$^2$ BMI have been excluded according to the limits of the BIA device.

### 3.2. Body composition analysis and densitometry

Body composition was defined by InBody 720 bioimpedance. The equipment measured the main body composition parameters: fat-free mass (FFM), skeletal muscle mass (SM), fat mass (FM), percent of body fat, visceral body fat, intra- and extracellulalar water (ECW, ICW), body cell mass (BCM), bone mineral content (BMC). We calculated BMI-analogue indices from the measured parameters to obtain weight-independent formulas. Fat-free mass index (FFMI) was considered to be altered <17 kg/m$^2$ in men and <15 kg/m$^2$ in women. Bone density was measured by DEXA (Hologic QDR 4500C).

ADA trough levels were measured by SHIKARI® Q-ADA enzim-immunoassay and anti-ADA antibodies were checked by SHIKARI® S-ATA. Malnutrition Universal

Screening Tool was used to evalute the risk of malnutrition based on ESPEN recommendations. Dietary intake was assessed by a dietitian and was recorded by Nutricomp DietCad®, a software validated to the Hungarian population. For data analysis SPSS statistics v22.0, Statistica 13.0 and MH Program 1.2. were used.

## 4. Results

A total of 173 IBD (126 CD, 47 UC) outpatients were included in study „A" to assess the risk of malnutrition and body composition. 37 patients (21.4%, CD: 28 [22.2%], UC: 9 [19.2%]) were at high risk of being malnourished according to the MUST questionnaire while 48 patients (27.8%; CD: 21 people [16.7%], UC: 5 people [10.6%]) were proven to have decreased FFMI by BIA. Among UC patients, we found that the rate of malnutrition risk was 19.1% (n=9), and an even higher proportion of patients were detected by low FFMI based on body composition analysis 23.4% (n=11). Among CD patients we found that the rate of being at risk of malnutrition was 22.2% (n=28) according to MUST scores and 29.4% (n=37) based on

FFMI. A higher proportion of small bowel involved CD patients were underweight compared to those with colonic involvement (14.3% vs. 4.0%), and they had more unfavorable body composition results as well (FFMI 16.91±2.41 vs. 18.24±2.56 kg/m$^2$, p=0.05 and BFMI (5.08±2.93 vs. 7.15±4.91 kg/m$^2$, p=0.004), respectively. Patients with stenosing type (n=14) showed the worst nutritional status according to FFMI (42.9%, n=6), or highest risk in MUST scale (57.1%, n=8).

We followed 198 IBD patients (144 CD, 54 UC) for 36 months in study „B". During the follow-up period, one patient died of septic complications of an abscess ectomy. 38 patients (n=19.2%) had BMI <18,5 kg/m$^2$, 88 (44.4%) patients were at normal range while 72 (36.4%) had high BMI. Based on FFMI 59 (29.8%) of the patients were at risk of sarcopenia. Patients with abnormally low BMI or low FFMI were more frequently hospitalized due to acute flare of the disease (low BMI vs normal: 23 vs. 22 p <0.005, sarcopenia risk vs. normal: 31 vs 30 cases, p <0.05) and spent significantly more days in hospital (BMI:

18.49 vs. 3.38 days, p <0.05; FFMI: 13.36 ± 34.2 days vs. 2.6 ± 6.4 days, p <0.005). The risk of IBD surgery was higher either in low BMI and FFMI cathegorie (BMI: 18 vs. 7, p<0.005; FFMI: 18 vs. 22 cases; p<0.05; resp.). Negative correlation was found between hopsitalized days and BMI (r=-0.48, p=0.001) and muscle parameters (FFMI: r=-0.43, p=0.07; SMI: r=-0.42, p=0.01).
Penalized logistic regression was used for the multivariate modelling of the outcome, and we found that hospitalization was positively associated with sarcopenia risk: alarming low FFMI was associated with an OR of 1.81 (95% CI: 1.03-3.20, p=0.04). Moreover, the risk of operation was lower in patients with normal BMI: OR=0.52 (95% CI: 0.29-0.93, p=0.02).

In study C, 40 IBD patients (33 CD- 7UC) were included. We observed that disease activity at week 0 differed significantly from the activity at weel 12 in the same subjects when marginal homogeneity was tested (Stuart-Maxwell chi-squared=15.2, df=2, p<0.001). According to our findings, baseline BMI and muscle parameters

increased significantly during the observed period (BMI: 23.80±7.18 vs. 24.50±7.33 kg/m$^2$; FFMI: 17.64±3.00 vs. 18.14±3.08 kg/m$^2$; $p<0.05$), while no significant changes were detected in the main body fat parameters (BFMI: 6.21±5.20 vs. 6.44±5.27 kg/m$^2$; $p>0.05$).

At the beginning of biological therapy, 30% (n=12) of the patients were at risk of sarcopenia regarding FFMI and 12.5% (n=5) regarding SMI. By the end of the induction therapy, the proportion of being at risk decreased to 25% (n=10) and 5% (n=2), respectively. As for the impact of different anti-TNF-alpha therapies on body composition, we found no significant difference between the effects of ADA vs. IFX treatment. Taking into account 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.

We observed significant differences in inflammatory laboratory parameters from week 0 (e.g. C-reactive protein 23.9 g/L) to week 16 (13.4 g/L, p=0.01).

Upon evaluating the dietary intake, we found that both the energy intake (20.19±7.64 vs. 26.05±9.21 kcal/kg; $p<0.001$) and the amount of main nutrient (protein: 0.92±0.38 vs. 1.13±0.51 g/kg; $p<0.001$, carbohydrate: 2.5±1.0 vs. 3.2±1.2 g/kg; $p<0.001$, fat: 0.57±0.33 vs. 0.98±0.38 g/kg; $p<00.1$) consumption improved significantly. However, the proportion of the mean nutrient intake did not change significantly during the observed period. No strong correlation was observed between the increased intake of protein and the muscle body composition parameters (ΔFFMI vs. Δprotein intake, $r=0.145$; $p=0.406$).

At the end of the 12 months observational period, 27 of 40 patients were on biologicals.

Baseline body composition and bone mineral content measuerd by BIA imporved significantly during the follow up, although a non-significant decrease was observed. (month 0, 3, 6 and 12: FFMI 17.64±3.00, 18.14±3.08, 18.18±2.98, 17.97±2.74 kg/m$^2$; BMC 2.90±0.62, 2.99±0.68, 2.95±0.61, 2.95±0.64 kg).

Based on BIA bone parameters, the rate of the patient who had altered bone mineral content decreased from 27.5% to 14.8% at the end of the follow up time.

We initiated ADA treatment (160/80/40EOW) in 18 IBD patients in study „D". ADA trough levels were measured at week 6 and 12.

We found a stable intra-patient ADA level (8.00 ±2.9 μg/mL and 7.73±3.14 μg/mL at week 6 and 12, respectively). However, the intra-patient changes of ADA trough levels showed a negative correlation with body surface area (r =- 0.682; p= 0.002). Moreover, intra-patient ADA level variability correlated negatively with the parameters indicating muscle content of the patients (FFMI: r = -0.494, p=0.045, SMI: r = -0.508, p=0.038).

## 5. Conclusions

In our reasearch, we evaluated nutritional status, risk of malnutrition and the prognostic role of altered body composition among our IBD outpatients.

We have also investigated anti-TNF-α's effect on body composition and the potential need to adapt the dose of biological therapy to body composition and physical capabilities. According to our results, the ratio of patients at risk defined of malnutrition by MUST score and defined by FFMI from the BIA measurements were notably different: while MUST indicated a risk of malnutrition in 1/5 of our patients (21.4%), BIA indicated the potential of sarcopenia in more than 1/4 of them (27.7%). According to our findings 23.5% of the patients who were in the normal BMI range had alarmingly low FFMI, and a further 9.3% of the patients had decreased FFMI although they were categorized to have low risk of malnutrition by the MUST scale. These results indicate that IBD patients are at risk for malnutrition, so screening methods should be a routine part of IBD care. If it is possible, malnutrition screening by MUST should be extended with body composition analysis. We suggest combining them in patients suffering from IBD.

According to our results malnutrition was proven to be a risk factor of more serious disease outcome. Patients with

low BMI and FFMI were more frequently hospitalized due to acute shub and spent more days in the hospital. Based on multivariate modelling of the outcome, alarmingly low FFMI was associated with an almost twofold risk of being hospitalized and and with low BMI the risk of an operation was one and half times higher.

We detected a significant improvement in the nutritional status of IBD patients during the induction phase of the anti-TNF-alpha therapy. According to our findings, baseline BMI increased significantly and the risk of sarcopenia based on FFMI decreased (from 30% to 25%) at the end of the induction period. Body composition was observed to change favorably during the follow-up period: body composition indexes indicate muscle content increased, but fat parameters did not change significantly. Based on BIA bone parameters, the percentage of the patient who had altered bone mineral content decreased almost to the half at the end of the follow up time. Analysing the dietary intake of the patients, we found that altough baseline energy, fat and carbohydrate intake was lower than among average healthy adults, it approached

the recommended amount following the induction phase. However, the energy proportion of the protein, fat and carbohydrate intake did not change significantly. At the end of the one-year follow-up period, a slight decrease was observed, but the improvement in muscle parameters was still significant compared to baseline values, while the change in fat parameters did not reach statistically significant levels. There was no difference in the effect on body composition between ADA and IFX. As far as we know, our study is the first to compare different anti-Tnf-α agents effect on body composition.

However, ADA is given in the same predetermined dose for everyone. Examining ADA trough levels variability, we found a stable intra-patient ADA level. The intra-patient changes of ADA trough levels showed a negative correlation with body surface area and parameters indicating muscle content of the patients.

With the results of our studies, we highlighted the importance of malnutrition among IBD patents. Our work has significant value for everyday clinical practice as the altered nutrition status and body composition can be

improved by the early introduction of appropriate nutrition therapy, and subsequent complications resulting from malnutrition may be eliminated.

## 6. Bibliography of the candidate's publications

### 6.1. Publications related to PhD thesis

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