Body composition and joint involvement related to functional well-being in pediatric inflammatory bowel disease

PhD thesis

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Budapest

2023

INTRODUCTION:

Inflammatory bowel disease (IBD) is a chronic, lifelong condition, causing recurring inflammation of the gastrointestinal (GI) tract. IBD affects almost every aspect of life, including physical, social, and emotional well-being. Its incidence is increasing in the pediatric population. As advanced therapy appeared, treatment goals have been changed: mucosal healing and improved health-related quality of life (HRQoL) become the targeted outcomes. Therefore, factors determining prognosis, such as nutritional status or physical activity (PA), and HRQoL are becoming outstandingly important.

Low skeletal muscle mass (SMM) can lead to increased morbidity and mortality, higher risk for relapses and infections, need for surgery, and complications after surgery. PA is important during childhood, as it improves bone structure, has a beneficial effect on the quality of life, also it can prevent several chronic illnesses. Moreover, during muscle contraction, anti-inflammatory myokines are released from muscles which are also positive for patients with IBD. PA and HRQoL also refer to the patient well-being.

HRQoL can be affected by joint involvement that is one of the most common extraintestinal manifestations (EIM) (14-22%) in IBD. Pain in the joints and restricted motion may have a negative impact on physical activity, social life and mood, and all these can contribute to impaired HRQoL

OBJECTIVES:

The primary aim of investigations was to collect data on body composition (BC) in children with IBD. In order to assess BC precisely we also measured BC of healthy controls for comparison. Moreover, assessment of PA, joint involvement, and HRQoL were also important additional aim of our studies. The main research questions and topics were the following:

1. Development of body composition Z scores and assessment of skeletal muscle loss in children with inflammatory bowel disease

a. The primary aim of this study was to identify the main determinants of BC parameters, especially SMM.
b. Based on our results we also aimed to develop BC Z scores to analyze BC parameters of patients with IBD
c. The secondary aim of this study was to assess SMM loss in the IBD group

2. Follow-up of body composition, physical activity, and health-related quality of life in children with inflammatory bowel disease treated with anti-TNF therapy

a. We set a goal to analyze BC, PA, and HRQoL in patients during anti-TNF therapy.
b. We also aimed to compare the PA of patients with IBD and healthy controls.
c. The secondary aim of this study was to analyze the baseline characteristics of patients with or without risk of sarcopenia at the beginning of anti-TNF therapy and to follow the changes in BC.

3. Frequency of joint involvement and health-related quality of life in patients with Crohn's disease

a. The primary aim of this study was to determine the prevalence of join involvement
b. The secondary aim was to analyze the association of joint involvement with disease activity and HRQoL

METHODS:

1. Development of body composition Z scores and assessment of skeletal muscle loss in children with inflammatory bowel disease

Study design

In this single center, cross sectional study, patients with IBD, diagnosed or treated at the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary were involved. Healthy controls were also included.

Subjects

Patients with inflammatory bowel disease

Fifty-seven patients diagnosed with pediatric IBD or starting anti-TNF therapy [(mean age: 14.2±2.7 years, 32 (56%) males, with CD (n=31) and UC (n=26)] were recruited in this study.

Exclusion criteria were concomitant conditions affecting BC (e.g., autism spectrum disorder, cirrhosis, edema, hypoalbuminemia, associated endocrine or chronic disorders (e.g., diabetes mellitus), known active malignancy, and fracture (e.g., leg fracture). Inclusion criteria were as follows: age between 10-18 years old, no exclusion criteria, and a signed informed consent form. All participants were of

the Caucasian race. Diagnosis for IBD was established based on the Porto criteria. Patients were treated according to the ESPGHAN guidelines.

Healthy control population

Healthy children and adolescents (n=307, mean age: 14.3±2.1) were involved. Children, with acute diseases, such as infections during the last 4 weeks before the evaluation, or known chronic disorders, cardiovascular diseases, obesity, physical disabilities, or lack of parental informed consent were excluded. From the 307 healthy children, 116 (mean age: 13.4 ± 2.2 years, 53 (45.7%) males) were measured in local primary and secondary schools, between 2007-2012 in the frame of a previous cohort study (OTKA 071730 National Scientific Research Fund, participating authors: GSR, OC.), (healthy control group A, (HC group A)). The remaining 191 (mean age: 14.8 ± 1.9 years, 91 (47.1%) males) were measured in 2017 in a local secondary school (healthy control group B, (HC group B)) with the same device.

Methods

Anthropometric parameters and body composition

Height was measured by trained staff using a validated fixed stadiometer. Weight and BC were measured using with a bioelectrical impedance analyzer (InBody 720 (Biospace Co, Ltd, Seoul, Korea)).

Data analysis and statistics

Data with normal distribution (anthropometric and laboratory parameters) were compared with the Student T test or with ANOVA

where appropriate. The Mann-Whitney U test was used for variance analysis for data with non-normal distribution. The associations between BC and anthropometric parameters were evaluated utilizing linear univariate and multivariate stepwise ridge regression models. Due to the dependence of BC data on age and BMI, a propensity score matching on a 1:1 basis of healthy children to IBD patients was performed. Then pairs of IBD patients and healthy children matched for age, sex, and BMI were formed.

After that, the LMS method was used to generate age, sex, and BMI normalized reference values. This method characterizes the distribution of a variable by its median (M), the coefficient of variation (S, ie, the ratio of the SD and mean), and skewness (L) required to transform the data to normality. To assess this, a maximum-likelihood curve-fitting algorithm to the original data plotted over the independent variable was performed. One set of table was created using BMI Z scores as an independent variable for determining BC Z score values in each percentile group. The Z score of a specific BC parameter (e.g. FFM, TBW, SMM or BFM) for an individual can be converted to the following SDS:

Z ie, $SDS=\{[Y/M(t)]^{L(t)}-1\}/[L(t) \times S(t)]$

where Y is the individual parameter of a child (BC parameter), and M(t), L(t), and S(t) are the specific values of L, M, and S interpolated for the BMI Z score of the same child.

During the analysis, less than 5% ($p<0.05$) probability was considered to statistically significant chance that the difference found is not a

coincidence. Data analysis was performed by using Statistica 8.0 (Stat. Soft. Inc).

2. Follow-up of body composition, physical activity, and health-related quality of life in children with inflammatory bowel disease treated with anti-TNF therapy

Study design

Patients with IBD starting anti-TNF therapy were consecutively involved in this single center, longitudinal, follow-up, observational study from September 2016 and April 2018 at the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary. BC, PA, HRQoL, disease activity, and laboratories were assessed at initiating anti-TNF therapy (measurement 0, M0), at the end of induction (M2), and 6 months (M6) in patients with CD and UC as well.

According to the secondary aim, patients were divided into two groups based on the baseline SMM Z score. Patients were considered to have a risk of sarcopenia when they had an SMM Z score $\leq$-1 when initiating anti-TNF therapy (Group risk of sarcopenia (Group RS); these patients were compared to children (Group normal SMM (Group NS)) whose baseline SMM Z score was > -1.

Subjects

All in all 32 patients with IBD, 21 with CD (age: 15.2±2.6 years (mean+SD), 9 male), and 11 with UC (age: 16.4±2.2 years, 5 male) were consecutively recruited in this study. Diagnosis and treatment were done as in our first study. Exclusion criteria were concomitant conditions affecting BC, PA, or HRQoL (e.g., autism spectrum

disorder or other mental diseases affecting writing or reading, age under 10 years (available Z scores for BC analysis), cirrhosis, edema, hypoalbuminemia, associated endocrine or chronic disorders, known active malignancy, fracture. Patients, who had to stop anti-TNF therapy were also excluded (hypersensitivity to IFX, surgery, or other reasons).

Methods

Anthropometric parameters and body composition

Anthropometric parameters and BC were measured as in the previous study discussed above. BC parameters were analyzed using BMI based Z scores, created from the healthy population earlier.

Assessment of physical activity

The Canadian Physical Activity Questionnaire for Older Children (PAQ-C) and Adolescents (PAQ-A) were adapted and then applied for the evaluation of PA. These questionnaires are self-administered, 7-day recall questionnaires, consisting of 10 questions, providing an activity score between 1-5 (1 represents low activity and 5 represents high activity level). As the questionnaire was completed by 204 healthy children as well, we had the opportunity to compare PA between patients with IBD and age-, sex, and BMI-matched controls. The ratio of the cases and controls was 1:3.

Assessment of health-related quality of life

For assessing HRQoL, the disease-specific Canadian IMPACT-III Quality of Life questionnaire was used. It consists of 35 questions, in six subscales (bowel symptoms, systemic symptoms, emotional

functioning, social functioning, body image, and treatment). Patients mark the statements to which they agree on a five-point Likert scale. Possible scores range from 35 to 175.

Statistical analysis

The general linear model was used to determine changes in each variable of BC, laboratories, and disease activity indices. Pearson's correlation coefficient was used for correlation probes. The level of significance was set at $p<0.05$. Non-continuous variables are shown as median (pc 25, 75). To compare continuous variables with parametric distribution, an independent t-test was applied. Non-parametric variables (results of questionnaires) were compared between groups with the Mann-Whitney U test. The Friedman test was performed to track changes in these variables, after that, a post hoc analysis with Wilcoxon signed rank test with a Bonferroni correction was applied, resulting in a significance level of $p <0.017$. All analyses were performed using IBM SPSS Statistics for Windows, version 20 (Chicago, IL).

3. Frequency of joint involvement and health-related quality of life in patients with Crohn's disease

Study design

In this observational prevalence study, patients were recruited by a gastroenterologist consecutively over 12 months (February 2011 to February 2012) at the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary. All subjects underwent a detailed musculoskeletal history and examination by a pediatric

rheumatologist (Beáta Dérfalvi) at the 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary. The maximum interval was 4 weeks between the gastroenterological and rheumatogological visits, and the condition of any patients did not deteriorated so markedly in the interim.

Subjects

Eighty-two patients (age: 13.7 ± 3.2 years (mean±SD), 1.2:2 male:female) with CD were involved. All patients with signed parental informed consent were included in the study. Patients diagnosis and treatment were done like in the previous studies.

Methods

Physical examination of the joints

First, the rheumatologist made a blinded musculoskeletal examination, to reduce the risk of examiner bias. Previous and/or ongoing musculoskeletal history and symptoms were only thereafter discussed with the patients. The physical examination was done according to the Spondyloarthritis Research Consortium of Canada Enthesitis Index. Active arthritis was defined as pain and/or limited range of motion with joint swelling. Previous "burned-out" arthritis was determined as a severely restricted range of motion with or without deformity. Arthralgia was specified as not exercise-related, localized, persistent joint pain at rest, with no evidence of arthritis. Patients who had arthritis in minimum one joint as well as arthralgia in other joint(s) were classified as having arthritis.

Assessment of health-related quality of life

To assess HRQoL, the Canadian IMPACT-III questionnaire, detailed above was filled out by the patients (if older than 7 years).

Statistical analysis

Parametric data were compared using Student's t-test. Comparisons of categorical variables were performed using Fisher's exact test. Chi logistic regression and chi-square test were used to examine any possible associations. A p-value of < 0.05 was considered significant. Calculations and statistical analysis were performed using IBM SPSS Statistics (version 21.0, IBM, Armonk, NY, USA).

Ethics

All of the studies were approved by the Medical Research Council Scientific and Research Ethics Committee and the Semmelweis University's Institutional Committee for Research Ethics. It was performed following the Declaration of Helsinki. All parent(s)/caregiver(s) and patients older than 7 years of age signed the informed consent.

RESULTS

1. Development of body composition Z scores and assessment of skeletal muscle loss in children with inflammatory bowel disease

Comparison of anthropometric and body composition parameters between patients with inflammatory bowel disease and healthy controls

Patients with IBD were at the same age, height, and height Z score as compared to the healthy cohort. Patients with IBD had statistically lower weight (in absolute values and Z scores also), (46.9±12 vs.

53.2±12.5 kg, and -0.5±1 vs. 0±0.8 Z score, $p<0.05$) and BMI (17.6±2.8 vs. 19.5±2.7 kg/m^2, and -0.7±0.9 vs. -0.2±0.8 Z score, $p<0.05$) than that of non-adjusted healthy children. SMM (22.3±8.4 vs. 24.4±6.3 kg, $p<0.05$) and FFM (38±9.8 vs. 43.8±10.7 kg) were lower in patients, meanwhile, BFM did not differ between these groups.

Determinants of body composition parameters

To analyze the relationship between BC, demographic, and anthropometric data, Pearson's correlation matrix was performed. The SMM, FFM TBW, and BFM were associated significantly with age (r=0.65; 0.64; 0.66; 0.21 $p<0.05$), sex (r=-0.35; -0.32 -0.35; 0.23; $p<0.05$), weight (r=0.9; 0,87; 0.91; 0.49; $p<0.05$), height (r=0.87; 0.87; 0.89; 0.17; $p<0.05$) and BMI (r=0.62; 0.58; 0.61; 0.66, respectively $p<0.05$).

The following step was the multivariate linear regression model, which was adjusted to age, sex, height, weight, and BMI. According to this, TBW and FFM are associated significantly with sex, weight, and BMI (TBW: ß= -0.16; 1.33 and -0.50; FFM: ß = -0.13; 1.46 and 0.62, respectively). SMM was associated significantly with all parameters (sex: ß=-0.17; age: ß= 0.05; height ß=-0.22; weight: ß= 1.54 and BMI: ß= -0.61) and BFM was associated with sex and BMI (ß= 0.27; 0.96, respectively).

Therefore, a stepwise ridged regression analysis was calculated and found that age, sex, and BMI are the main significant determinants of SMM (ß= 0.45; -0.31; 0.38 $p<0.05$ respectively), TBW (ß= 0.46; -0.31; 0.38 $p<0.05$ respectively) and FFM (ß= 0.45; -0.28; 0.35, $p<0.05$

respectively). The main determinants of BFM were sex and BMI (ß=0.25; 0.39 $p<0.05$ respectively).

Creating BMI based Z scores

Based on these, a propensity score matched control population was created. Comparing patients with the propensity score matched controls, we found no difference in SMM and BFM, while TBW and FFM still differed significantly. Therefore, to show whether patients with IBD have a real lower muscle mass featured by SMM, without using propensity score matching, BMI Z score based BC Z score calculation was implemented. BMI Z score based LMS values were determined, and percentile boundaries were calculated and plotted by normalizing to age, sex and BMI. An individual child's BC Z score value was calculated according to the equation above in the statistics section.

Application of skeletal mnuscle mass Z score in children with inflammatory bowel disease

Despite the different laboratory parameters between CD and UC group, there was no significant difference in terms of body size and BC parameters.

2. Follow-up of body composition, physical activity, and health-related quality of life in children with inflammatory bowel disease treated with anti-TNF therapy

Body composition at the initiation of anti-TNF therapy

At baseline, height, weight, BMI and even BFM Z scores did not differ between patients with CD or UC, however, patients with CD had

significantly lower FFM Z scores compared to patients with UC (-0.4 vs 0.5 p=0.04).

Body composition during the first six months of anti-TNF therapy

During six months following anti-TNF therapy, mean height, weight, and BMI Z scores did not change. There was a significant increase in FFM Z score in patients with CD (M0: -0.3±1.2. M2: -0.1±1.1. M6: 0.1±1.2. $p<0.05$), but not in patients with UC (M0: 0.8±1.3. M2: 0.8±1.1. M6: 0.8±1.1).

Health-related quality of life during the first six months of anti-TNF therapy

At the initiation of anti-TNF therapy, the median IMPACT-III score was 128.5 (pc 25;75: 111.5;137.8) in patients with CD and 109 (pc 25;75: 83;129) in patients with UC. The changes in HRQoL did not reach the level of significance.

Physical activity during the first six months of anti-TNF therapy

PA was lower in patients with CD compared to age-, sex, and corresponding BMI-matched healthy controls (CD: 1.1 vs. controls: 2.4), however, PA level of patients was comparable to the PA level of matched controls (2.3 vs. 2.4) by M6. PA among UC patients did not differ from controls, and it remained the same throughout the study period (M0: 1.6 vs. 2.3. M6: 1.8 vs. 2.2).

Comparison of children with or without risk of sarcopenia

Patients with a risk of sarcopenia (Group RS) were significantly younger and shorter compared to patients without a risk of sarcopenia (Group NS), (Group RS vs. Group NS, age: 13.9±2.8 years vs.

16.4±1.9 years, p<0.05; height Z score: -0.7±1.1 vs. 0.4±1.0, p<0.05, respectively) at baseline. We could not detect a difference in disease duration, activity indices, any of the laboratory parameters, HRQoL, or PA between the two groups. At M2 and M6, the statistical difference in height Z scores became comparable between the two groups (Group RS vs. Group NS; M2: -0.8±1.3 vs. 0.4±1.0, M6: -0.4±1.2 vs. 0.4±1.1). Patients with a risk of sarcopenia had an increasing SMM Z score during the anti-TNF therapy, however, their SMM Z score was still statistically lower at M2 and M6 than children in Group NS. SMM Z score did not change in Group NS.

3. Frequency of joint involvement and health-related quality of life in patients with Crohn's disease

Prevalence of arthritis

Thirty-five percent (29/82) of the patients had objective arthritis (at the examination or before that). Arthritis was diagnosed in 24 cases based on physical examination (point prevalence), and 5 patients had a remote history of documented active arthritis, without having a remaining restricted range of joint motions or contractions (period prevalence).

Prevalence of arthralgia

39/82 patients had evidence of arthralgia during the entire course of the disease, which results in 48% (39/82) as the cumulative incidence of arthralgia in this patient population. Of these patients, 8/39 (22%) had only arthralgia, without arthritis. The most affected joints were the knee and ankles.

Joint involvement and its association with health-related quality of life and disease activity

Patients having joint involvement (arthritis or arthralgia) had lower HRQoL, compared to patients without joint involvement. These patients also had higher PCDAI values.

CONCLUSIONS

Based on our studies, we can draw the following conclusions:

1. Based on our calculations, BC parameters depend on age, sex, and body size, therefore BC parameters have to be normalized by BMI Z score due to its dependence on changes in body size with aging. BMI normalized SMM Z score may serve as an objective estimation of muscle loss in children with chronic wasting diseases.

2. We provided a BMI normalized SMM Z score that is applicable in everyday clinical practice.

3. We have verified a significant improvement in FFM Z scores in children with CD during anti-TNF therapy without the changes in weight and BMI Z scores. This highlights the fact, that weight and BMI are not enough sensitive markers for assessing nutritional status.

4. We found a significant improvement in FFM Z scores in children with CD during anti-TNF therapy that refers to the beneficial effects of anti-TNF therapy on nutritional status.

5. PA of patients with CD achieved the level of PA of healthy controls, which could be considered as a part of optimal recovery.

6. The lower age of patients with a risk of sarcopenia draws attention to the vulnerability of younger patients. Children in the early puberty are in the active phase of growth, also it seems, that they are vulnerable to the factors determining the development of SMM as well.

7. We also verified that the prevalence of arthritis and arthralgia (35% and 48%, respectively) is much higher than recognized by the gastroenterologist (arthritis: 3-24%, and arthralgia:14-22%) in pediatric CD.

8. As joint involvement can affect the HRQoL of patients with IBD, referring patients to a pediatric rheumatologist might be beneficial, by increasing symptom control, quality of care, and therapeutic management in these patients.

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