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

PhD thesis

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LIST OF ABBREVIATION

AZA	Azathioprine
BFM	Body fat mass
BIA	Bioelectrical impedance analyzis
BMI	Body mass index
CD	Crohn’s disease
ECW	Extracellular water
EIM	Extraintestinal manifestation
FFM	Fat free mass
GI	Gastrointestinal
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
ICW	Intracellular water
IFX	Infliximab
LM	Lean mass
MF-BIA	Multi frequency bioelectrical impedance analyzis
MTX	Methotrexate
PA	Physical activity
PAQ	Physical activity questionnaire
PCDAI	Pediatric Crohn’s disease activity index
PUCAI	Pediatric Ulcerative colitis activity index
SF-BIA	Single-frequency bioelectrical impedance analyzis
SMM	Skeletal muscle mass
TBW	Total body water
TNF-α	Tumor necrosis alpha
UC	Ulcerative colitis

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1. INTRODUCTION

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

Malnutrition and sarcopenia can lead to increased morbidity and mortality, higher risk for relapses and infections, need for surgery, and complications after surgery in IBD. 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 well-being of children with IBD.

HRQoL can be affected by joint involvement, which is one of the most common extraintestinal manifestations (EIM) (14-22%). Presumably, social inactivity due to the pain, restricted motion in the joints may be associated with impaired HRQoL in addition, the physical inactivity may contribute to the altered body composition (BC), as well.

Despite HRQoL and nutritional status are considered essential factors to be monitored in IBD care, there is a lack of studies investigating the association of HRQoL, BC and PA, therefore our aim was to investigate the relationship of these. Furthermore, as joint involvement affects HRQoL and PA, we also analyzed the burden of joint involvement in pediatric IBD.

1.1. Inflammatory bowel disease

IBD is a lifelong, destructive condition of the GI tract, caused by chronic inflammation, resulting in variable periods of remission and relapses (1). Two major subtypes are CD and UC. In some cases a clear diagnosis can not be established. These patients get the diagnosis of IBD-unclassified, mostly, these patients later will have a definitive diagnosis as CD or UC (2).

1.1.1. Epidemiology

Since the middle of the 20th century, the incidence of IBD is increasing, which can be seen in the pediatric population, as well. The highest incidence of CD are in the Central- and Western European countries, and in the USA (0-15.3/10^5), and that of UC in the Northern European countries (0-14.8/10^5) (3). According to the Hungarian Pediatric IBD Register (HUPIR), in Hungary, the incidence is 4.7/10^5 and 2.3/10^5 in patients with CD and UC, respectively (4).

1.1.2. Etiology

Unfortunately, the exact etiology of IBD is still unknown. Based on our current knowledge, there are four factors considered to be essential in the pathogenesis of IBD (5,6). Firstly, genes playing role in autophagy, phagocytosis, barrier function, adaptive and innate immunity, antigen presentation, and also epigenetic factors play important role (7–10). Secondly, important factor is the imbalance in regulators and effectors of the immune system. Accumulation of T helper cells in the intestinal tract, leads to the production of proinflammatory interferon-γ and tumor necrosis factor-α (TNF-α) (11). Thirdly, environmental factors, such as breastfeeding, smoking during pregnancy, antibiotic use in early life, use of breastmilk, and diet containing a lot of fat and carbohydrates, or frequent use of food additives, emulsifiers (carboxymethyl cellulose) can play role in the pathogenesis of IBD (12,13). Finally, the microbiome as an internal environmental factor seems to be the most important etiological factor of IBD. The dysbiosis in IBD can be characterized with decreased bacterial diversity and the decreased amount of anaerobes and Lactobacillus species. More and more data is being collected about role of the disturbed the viral and fungal microbiota of the intestine, as well (14).

1.1.3. Clinical features

In CD, the inflammation can spread to the entire intestinal wall and can be present in the whole GI tract, leading to inflamed and noninflamed parts (skipping lesions) in the gut. In pediatric patients, the most common disease location is the ileocolonic region (35-50%) (15). In contrast, UC affects the mucosa and submucosa of the rectum and colon, leading to continuous inflammation. Sometimes, the whole colon (pancolitis) or even the terminal ileum is affected, leading to backwash ileitis, which can cause severe problems at differential diagnosis.

The main symptoms of IBD are chronic abdominal pain, diarrhea, bloody stool (more common in UC), weight loss, loss of appetite, fatigue, subfebrility, perianal fissure or fistula, abscess, and skin tags. In childhood, the initial symptoms can be atypical or less specific, like pubertal delay or growth impairment. Sometimes only EIMs precede the intestinal sympoms (16,17). Complications including strictures, fistulae, and abscesses occur more frequent in CD (18). The main complication of UC is acute, severe colitis, that is a life-theratining condition.

1.1.4. Extraintestinal manifestations

In about one-third of the patients, the symptoms can be more severe because of the EIMs of the disease (19). The most common EIMs are arthropathies. They usually occur before (up to 4%) or within the first year after the GI symptoms present (20–22). The clinical manifestation varies, including asymmetrical, transitory, and migratory arthritis (pauciarticular or polyarticular), peripheral joint pain, and spondyloarthropathy.

IBD can also affect the mouth (aphthae), skin (erythema nodosum, pyoderma gangrenosum), and eyes (episcleritis, anterior uveitis) (19). The liver also can be affected – in 2-5% of the IBD patients sclerosing cholangitis develop, which is more common in patients with UC. Other liver diseases, such as autoimmune hepatitis, primer biliary cirrhosis, and cholelithiasis can also develop (23). There is also an elevated risk of developing pancreatitis (24).

1.1.5. Diagnosis

The diagnosis is based on the Porto criteria (1). According to Porto criteria, diagnostic workup requires proper physical examination (e.g. abdominal tenderness, fissure, fistule, EIM), stool culture, laboratory parameters (elevated inflammatory markers, anemia, iron, vitamin B_{12} deficit, thrombocytosis), and abdominal ultrasound. Immunoserology, more precisely Anti-Saccharomyces cerevisiae antibody, which is more common in CD, or anti-neutrophil cytoplasmatic antibody, more common in UC, can also help to establish the diagnosis. Fecal calprotectin can be used to measure the activity of intestinal inflammation (25).

The panendoscopy is essential in the diagnostic workup. In case of CD, longitudinal ulcers, cobblestone appearance, and aphthous ulcers are characteristic. In UC, the characteristic features are erythema, vascular marking, erosions, ulcers, bleeding, and

pseudopolyps (26). This can be further enhanced by histopathological examination of biopsies, on which the presence of granulomas in case of CD can confirm the diagnosis. Typical histopathology signs for UC are cryptitis and crypt abscesses (27). MR enterography can help to assess the involvement of the small intestine, the presence of EIMs and sometimes fissures, fistulas, and abscesses are also visible (28).

The clinical phenotype, more precisely, the intestinal involvement is associated with prognosis. In pediatric patients with IBD, the Paris classification is used for the classification of phenotype (29). In CD, it is based on the age at diagnosis (<10 years, 10-17 years, 17-40 years, or > 40 years), location of the inflammation (distal 1/3 ileum ±, limited cecal disease, colonic, ileocolonic, upper disease proximal to Ligament of Treitz or upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum), the behavior of the disease (non-stricturing non-penetrating, stricturing, penetrating, both stricturing and penetrating or perianal disease) and affection on growth (no evidence of growth delay or present of growth delay). In UC, the classification focuses on the extent (proctitis, left-sided UC (distal to splenic flexure or proximal to splenic flexure), and severity (never severe, ever severe) of the disease (29).

1.1.6. Disease activity index

The disease activity in children can be monitored by disease activity indeces. The activity of CD can be monitored with the Pediatric Crohn's Disease Activity Index (PCDAI) (30). It includes questions about current symptoms, the physical examination, and also laboratory tests. Scores range from 0 to 100, the higher score reflects a more active disease. A PCDAI score <10 reflects inactive disease, between 10 and 30 mild disease, and a PCDAI score ≥30 indicates active disease (31).

Disease activity of UC is calculated with the Pediatric Ulcerative Colitis Activity Index (PUCAI) (32). It is a 6-item questionnaire including only clinical symptoms, with a score range of 0-85, the higher score indicates more severe disease activity. PUCAI score < 10 points indicates remission, between 10 to 34 reflects mild, between 35-64 moderate, and over 65 points indicate severe disease.

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1.1.7. Treatment

The main goals of treatment are mucosal healing, appropriate HRQoL, and growth. There are international guidelines available to support the treatment of children with IBD

According to ESPGHAN-ECCO joint guideline, the induction therapy in pediatric CD is exclusive enteral nutrition (EEN), a special liquid diet, with the exclusion of other dietary components, lasting through 6-8 weeks (33). It is a good alternative to systemic steroids, without severe side effects. Steroids can be also used in moderate and severe disease mostly in patients, for whom EEN is not suitable. As a promising alternative to EEN, partial enteral nutrition and the Crohn's disease exclusion diet is also spreading, when the patients are allowed to eat certain foods in a certain amount and drink the special formula (34). In patients with UC, 5-aminosalicylates (in mild disease severity) or steroids (moderate–severe) can be used as induction therapy (35).

As maintenance therapy, immunomodulators, such as azathioprine (AZA), and methotrexate (MTX) are used in both CD and UC. In UC, aminosalicylates can also be recommended for this purpose.

The initiation of biologicals, such as anti-tumor necrosis factor alpha (anti-TNF alpha) therapies were game changers in the therapy of IBD. Anti-TNF therapy can be used in case of severe disease and perianal disease as induction therapy and in case of refractory disease to conservative therapy. Two types of anti-TNF therapy are available for children with IBD in Hungary: infliximab (IFX) (available from 2007) is a chimeric human-murine monoclonal antibody, and adalimumab (ADA) (available from 2014) which is a humanized anti-TNF alpha antibody. In some cases anti-TNF therapy is not effective due to primary nonresponse - when the inflammation is not TNF mediated - or due to loss of response - immunogenicity resulting in the formation of antibodies against the TNF alpha antagonists. In these patients new, upcoming therapies are available, such as vedolizumab, ustekinumab or tofacitinib.

Surgical treatment is also part of the treatment. In special cases, like severe penetrating, strituring disease, perforation, fistulae, perianal disease or abscess or growth delay, surgical intervention is also needed in CD. In case of UC, colectomy may be indicated in severe acute colitis and therapy refractory chronic colitis (36).

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1.2. Nutritional status, body composition, and its assessment

1.2.1. Malnutrition in inflammatory bowel disease

The imbalance of energy, protein, and other nutrients can lead to malnutrition that is associated with impairment on physical and emotional well-being, clinical outcome, HRQoL, and body form (for instance BC), such as loss of lean mass (LM), fat free mass (FFM), or skeletal muscle mass (SMM), even with normal body mass index (BMI) (37–40).

Nutrition has been implicated in all aspects of IBD, such as pathogenesis, diagnosis, treatment, and prognosis (33,41–46). Nutritional therapy such as EEN or partial enteral nutrition with dietary counseling is an important cornerstone of patient management. Moreover, growing evidence suggests that malnutrition is related to growth failure, impaired bone structure, disrupted pubertal development, increased complication rates, and poor prognosis (45–47).

Despite a lot of research, the real prevalence of malnutrition is still lacking, as it varies from report to report, depending on the methods used for assessing nutritional status, and patients involved in the study (in- or outpatients) (48).

1.2.2. Factors leading to malnutrition in patients with inflammatory bowel disease

Several factors can lead to malnutrition in patients with IBD. Some of them are due to chronic inflammation, others are specific consequences of the disease itself.

Through nausea, abdominal pain, and vomiting, IBD itself can lead to decreased oral food intake. Due to vitamin, mineral deficiencies, and pro-inflammatory mediators (TNF-α, interferon-γ, interleukin-1, and 6), alteration in taste also can contribute to anorexia. Anorexigenic effect of drugs, hospitalizations and prolonged restrictive diets are also risk factors for undernutrition (49,50).

Another important factor is malabsorption and nutrient loss. The main causes are loss of epithelial integrity, impaired epithelial transport, bacterial overgrowth, and increased intestinal motility. The reduction of absorptive surfaces such as intestinal resection, enteric fistulas, and villous hypertrophy also take part. Inflammatory cytokines released by immune cells within gut mucosa also correlate with malabsorption (50–52). Through the ulcers, chronic blood, and protein loss can cause anemia and hypoalbuminemia (51). In cases of the affected terminal ileum, biliary salt diarrhea can

develop, leading to impaired absorption of fat-soluble vitamins and lipids, fat malabsorption, and steatorrhea (50).

According to energy and nutrient metabolism, the literature is controversial. Raised, unchanged, even reduced energy expenditure can be explained theoretically, as patients with decreased oral intake could have decreased energy expenditure, however, inflammatory processes can lead to increased energy expenditure (53–57).

In addition to their potential anorexigenic effect, medications can affect micronutrient absorption and utilization. Glucocorticoids interfere with the utilization and absorption of phosphorus, zinc, and calcium, as well as impair the metabolism of vitamin C and D, and also influence protein catabolism. Long-term sulfasalazine therapy, as it is a folic antagonist (like MTX as well), can lead to anemia and hyperhomocysteinemia (58).

1.2.3. Sarcopenia

Malnutrition is a strong predictor of the onset of sarcopenia, which is one component of malnutrition (59). In adults, it has been defined by the loss of SMM (with exact cut off values) and reduced muscle strength or physical performance (60). The main factors in its pathophysiology are decreased nutrient intake, the lack of PA, and the large amounts of inflammatory cytokines (61). Its influence on clinical outcomes has been only recently recognized in the pediatric population, however, research in the pediatric field is limited due to the lack of definition of sarcopenia and reference values of SMM in children (62). Understanding and assessment of sarcopenia would be really important, as it may have an impact on growth, neurocognitive development, and quality of life, therefore targeted nutrition support and proper rehabilitation interventions would be beneficial for these patients (62). In patients with IBD, sarcopenia can be a predictor for adverse clinical outcomes and affects postoperative complications (39,63). Adequate prevention could prevent subsequent complications, such as the increased risk of requiring surgery, high rate of major postoperative complications, abscesses, longer hospital stays, and increased risk of infections (64).

1.2.4. Body composition

There are no gold standard laboratory parameters, values, or techniques for evaluating nutritional status. Data about energy balance (caloric intake, energy

expenditure), anthropometrics (height, weight, BMI), laboratory parameters (anemia, total protein, albumin, lipids, trace element, vitamin deficiencies) clinical evaluation, and BC analysis can help in this manner.

Earlier, BMI was a key factor in the assessment of nutritional status. Nowadays, growing evidence suggests, that the impact of BMI is limited. Although there is an association between BMI and the percentage of fat mass in overweight patients, BMI seems to be inappropriate as a proxy for fat mass (65). Also, in normal and underweight women BMI can mask various types of BC deficits, questioning its role in characterizing underweight (66). Studies in IBD patients also found differences in BC parameters and changes in BMI, mostly decreases in LM or body cell mass, despite normal BMI (67). As BMI is not able to discriminate between excess body fat and increased LM, is not able to get a reliable picture of the subjects' nutritional status (68).

Therefore, BC analysis is one of the main cornerstones to evaluate the responses to internal and external factors affecting nutritional status (68). There are about 30-40 different body components, which can be grouped by different levels. We can speak about the “atomic level” (11 major elements), the “molecular level” (water, protein, carbohydrates, bone minerals, soft tissue minerals, and lipids), the “cellular level” (cell mass (which can be divided into fat and actively metabolizing body cell mass), extracellular fluids, and extracellular solids), and the “tissue-organ level” (skeletal muscle, visceral organs, bone, and adipose tissue) of BC. Finally, the “whole body level” means the brain, trunk, upper and lower limbs (69).

In clinical settings , the two component model, which differentiates the body into fat mass (which consists of the visceral and subcutaneous adipose tissue), and FMM, (the actively metabolizing part of the body) is still very popular (70). FFM contains the total body water (TBW, including intra- and extracellular water (IWC and ECW), the bone tissue and proteins (total body protein / visceral protein), and essential lipids (as they are responsible for cellular physiology and reproductive function, for instance, phospholipids) as well. In a lot of studies, the main outcome is body cell mass, which is also a part of FFM and it is the active cell mass of the body, including total body protein and ICW. In the literature, LM is also an frequently used parameter, mostly as a synonym for FFM. The difference between the two compartments is in the essential lipids, as LM does not contain them. As the weight of essential lipids is negligible, and the function of

the two compartments is almost essential, both of them (FFM and LM) are good indicators for expressing the metabolically active part of the body (71). For expressing SMM (also part of FFM or LM), mostly whole body SMM (via bioelectrical impedance analyzis (BIA)) or muscle cross sectional area (measured by peripheral quantitative computed tomography) is used. Schematic diagram about the main BC compartments are in Figure 1 (71).

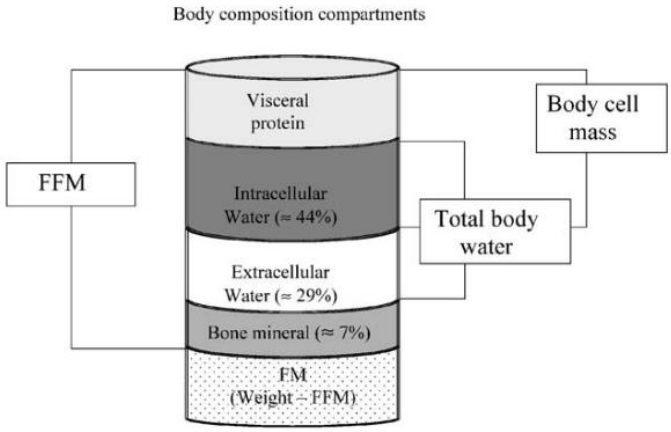

Figure 1. Schematic diagram about the main body composition compartments (71).

1.2.5. Regulation of body composition compartments

The individual BC compartments are interrelated through hormonal regulation and cell-signaling networks, influencing the activation and development of each other (58,68). Pathological conditions can alter the balance leading to altered regulation of metabolism and BC.

SMM takes part in the metabolism of glucose and protein turnover. Muscle growth is regulated by the insulin/growth hormone/insulin-like growth factor 1 pathway. In chronic inflammation, the elevated TNF-α and interleukin-6 cause growth hormon resistance in the liver and muscles, leading to protein degradation and inhibiting cellular growth, with subsequent reduction of myofibrillar proteins. It can also activate myostatin, a member of the transforming growth factor-beta family, which induces the degradation of sarcomeric proteins. All of this results in loss of muscle mass and impaired muscular contraction (58).

Adipose tissue has also an important role in the modulation and regulation of metabolism. It has a special role in IBD, especially in CD, as “creeping” fat, a mesenteric

fat that is often present in patients with IBD correlating with transmural inflammation and further complications such as strictures, fistulas (72,73). This type of adipose tissue does not depend on BMI. The mesenteric fat produces proinflammatory cytokines such as TNF-α, interferon-γ, interleukin-6, interleukin-1, and adipokines such as leptin and resistin. Leptin stimulates the proliferation of blood mononuclear and CD4+ T cells and promotes the development of Th1 response (74). Bacterial lipopolysaccharides induce resistin, which promotes the secretion of TNF-α and interleukin-12, activates mononuclear cells, and interact with bone mass, as well (75).

Bone mass is also influenced by resistin, as it increases the number of differentiated osteoclasts, leading to impaired bone loss. Also, adiponectin has a negative correlation with bone mass. Chronic inflammation can also alter the balance between osteoblasts and osteoclasts (58,76,77). TNF-α, interleukin-1, and interleukin-6 induce receptor activator nuclear factor kappa-β ligand, promoting bone reabsorption through osteoclasts (58,76,77).

1.2.6. Assessment of body composition – measurement techniques

In the assessment of BC, considering anthropometrical data, such as weight, height, BMI, and body circumferences are important. However, the full characterization of BC compartments is possible only with special techniques.

To measure BC, several non-invasive techniques exist. Certainly all of them have their pros and cons. Total body potassium (using ^{40}K isotope), neutron activation, total body pletysmography, isotope dilution (D_2O dilution or ^{18}O) and MRI are reliable techniques, give precise information, however they are expensive, need special equipment, and their use requires special knowledge. CT gives also precise quantitative and qualitative information about BC, however, due to the radiation, high-cost, and need for expert knowledge, its everyday use may be limited. Ultrasound can also be used for measuring subcutaneous and visceral fat mass, as it is quick, cheap, portable and reliable, however it needs specialist, and the anatomical variants can influence the outcomes. Skinfold thickness measurement is another easy and inexpensive method for measuring fat mass, but a lot of estimations are needed, and the ratio of subcutaneous and total body fat remains uncertain (78). Dual-energy x-ray absorptiometry (DEXA) is a widespread technique. It is a reliable tool to estimate soft tissue, lean tissue, bone, and fat. On the other hand, it is expensive and includes radiation exposure, however, it is much less than

a CT scan and the radiation dose is not more than one received during a high-altitude transcontinental air flight (79,80).

Bioelectrical impedance analysis (BIA) is based on the fact, that hydrated tissues conduct electricity. The method became more and more popular, as it is a non-invasive, safe, easy-to-use, quick bedside method, the devices are portable, and the results are reproducible and easily evaluated (71). The technique is based on the different electrical conductivity of tissues. The body water conducts electricity very easily, fat tissue behaves like an insulator. During BC analysis, a weak alternating current electric field is generated via the electrodes. The resulting voltage drop is measurable. The resistance level of the tissues against the current can be described with the impedance, which is calculated from the bioelectrical charge and strength of the current. The impedance is composed of two types of resistance: the resistive resistance (R, the ability of the biological structures to "resist" the passage of electricity) of the electrolyte containing intra- and extracellular fluid, and the capacitive resistance, the reactance (Xc, the opposing force to electricity) which is produced by the cell membranes. Resistance is inversely proportional to the water content, which means, that lean tissues are good conductors (because of their water and electrolytes content) and have high reactance, while fat tissues are poor conductors and have low reactance (58,71).

At lower frequencies, the current does not penetrate the cell membranes, so it will be able to pass through only the extracellular space. At 50 kHz, the current can pass through both the intra- and extracellular fluid, with a variable proportion from tissue to tissue. The relationship between resistance and reactance is influenced by the electrical properties of tissues, which can be affected by nutritional and hydration status. Phase angle is a parameter describing this relationship, and it can predict clinical outcomes (71,81). Lower phase angle is associated with sarcopenia, while higher indicates muscle hypertrophy (58). Furthermore, when resistance and reactance are plotted graphically after standardizing for height (bioelectric impedance vector analysis), different conditions can be read (82,83).

There are different methods of BIA. The single frequency (SF-BIA) is one of the oldest methods, which is available since the 1990s. Most single-frequency BIA analyzer operates at 50 kHz. It provides information about the weighted sum of extra- and intracellular water (ICW and ECW). Different empirical equations are applied to calculate

FFM. These equations have been derived in healthy subjects, subsequently, SF-BIA is not able to give reliable information in conditions affecting the hydration status (71). Multi-frequency BIA (MF-BIA) uses multiple frequencies (0, 1, 5, 50, 100, 200 to 500 kHz) to assess FFM, TBW, ICW, and ECW. It is more reliable and less biased compared to SF-BIA for the prediction of ECW, while SF-BIA is more accurate and less biased for estimating TBW in critically ill subjects (84,85). Recently, segmental BIA is spreading, which measures different segments (trunk and the 4 limbs) on multi-frequency. The need for segmental BIA measurement is shown by the different behavior of the trunk compared to the limbs. The trunk of the body contributes only a little (about 10%) to the whole body impedance, while it represents about 50% of the whole body mass (86). This suggests that with whole-body BIA, the changes of the impedance are related either to changes in the FFM, or muscle mass of the limbs. Also, changes in the FFM (or muscle mass) of the trunk are not adequately described. Finally, even large changes in the fluid volume within the abdomen have a minor influence on FFM in whole-body BIA (87,88).

All in all, BIA is a good tool for the evaluation of BC in healthy subjects and in patients with chronic diseases via validated BIA equations, that are appropriate concerning age, sex, and race. During the measurement, proper conditions (fasting, voided bladder, minimal clothing, room temperature, abduction of limbs) have a high importance. In patients with extreme BMI ranges and with abnormal hydration status MF-BIA may have advantages over SF-BIA. For longitudinal follow up, it is best to use in patients with normal hydration and with a BMI between 16-34 kg/m^2 (89). As due to the different body shape, BC parameters can differ between sex, race, and different age groups, especially in childhood, population-specific percentiles/cut-off values are needed to interpret data (90).

1.2.7. Assessment and monitoring of anthropometric parameters in children

For comparison of pediatric anthopometric parameters, percentiles and Z scores are used. Percentiles are the percentage of observations (or population) that falls below the value of a variable. They are non-continuous variables, however, they are intuitively more understandable and they indicate the expected prevalence. Unfortunately, they are not comparable across different anthropometrics, we can not determine the extreme values with percentiles (91). Z score is a number of standard deviation (SD) away from the mean when the distribution is normal. They are standardized quantities, so they are

comparable across ages and sexes and can be analyzed as continuous variables. Nevertheless, they can quantify extreme growth status at both ends of the distribution, and are useful in assessment of longitudinal changes in anthropometric status (91). In Hungary, Kalman Joubert et al. developed a database for children from 0 to 18 years, to calculate their percentiles or standard deviation scores (92).

1.2.8. Body composition in children with inflammatory bowel disease

In the majority of pediatric studies, patients, especially with CD, have reduced LM or FFM compared to controls (93–96). Several studies showed lower LM in patients with active CD, which deficit remained during the follow up (55,96–101). In studies where the deficit remained in the inactive phase, as well (102), findings could be influenced by systemic steroids (100,102,103). According to therapy, Thayu et al. found greater improvements in LM on IFX therapy (100). Gerasimidis et al. reported increased LM after EEN therapy, reaching the reference values after the treatment (101). Interestingly, high-dose corticosteroid therapy resulted in a significant increase in whole protein breakdown and loss, even in short term in children with CD, which could explain why LM deficit remains on concomitant steroid therapy (104). Comparing CD and UC patients, protein-related compartments seem not to differ (105–107).

Regarding muscle mass, most of the studies showed reduced quantity (103,106,108,109). In the study of Dubner et al., the deficit of muscle mass persisted after 12 months of treatment (108).

Much less studies evaluated BFM. Present studies involving mostly patients with CD, showed no difference in BFM of patients with IBD compared to controls. In the study of Thayu et al., female patients with CD had decreased BFM, as well (99,100). In connection with BFM and disease activity, data are controversial. Some studies reported lower fat-related compartments in patients with active disease, while others did not (55,96,99,101). In inactive disease, most of the studies found no difference in patients with IBD (102). Comparing CD and UC patients, patients with CD had lower BFM compared to patients with UC (105,110). In the study of Thayu et al., increase in BFM was associated with cumulative corticosteroid dose. The heterogeneity of the patients in different studies results in difficulties to draw clear conclusions.

1.3. Physical activity in inflammatory bowel disease

Recent evidence suggests that during PA, myokines (interleukin-15) releas from muscle mass, which has an anti-inflammatory effect, inhibiting adipocytokines and macrophage mediators produced by visceral fat. However, this communication is two-way, as visceral fat can inhibit the myokine release from muscle mass (111,112).

Speaking about PA, several concepts arise, as PA can differ in type (e.g. endurance vs. resistance training), intensity, duration, and frequency. Intensive exercise can induce transient mild systemic inflammation (113). On the other hand, regular exercise training increases resistance to infections (114).

Among IBD patients, regular exercise was found to be beneficial for the symptoms of IBD, however because of increasing disease severity and complaints on the severity of symptoms they stop exercising (115). Moderate exercise (walking or yoga) was verified to be optimal for QoL and to reduce stress level in patients with quiescent or mildly active disease. as well (116).

Measuring PA, especially inchildhood, is challenging. Direct observation and indirect calorimetry are the most reliable methods, however, they hold important drawbacks. Activity monitors (pedometers and accelerometers) and heart rate monitoring are objective methods, but specific devices are needed (117). In given circumstances questionnaires are the most feasible methods, however, it is a subjective method.

1.4. Health-related quality of life in inflammatory bowel disease

With the growing prevalence of chronic diseases and increased life expectancy of these patients, improved HRQoL became one of the main treatment goals in patient care.

Pain, treatments, and disadvantages due to the illness (e.g. absence from school, frequent bowel movements, dietary restrictions) place a great psychological burden on the patient. Moreover, previous studies showed, that there is a meaningful interaction between the immune system and the brain, meaning, that immunologic processes influence emotion regulation as well, through changes in neurochemistry, neuroendocrinology, and behavior (118).

The most widely used instrument among pediatric IBD patients with good reliability and validity is the IMPACT-III questionnaire (119). The final form was reached through multiple transformations. The different questionnaires contain questions in the same

domains, but there is a difference in the number of questions. The latest version of the IMPACT questionnaires (IMPACT-III) contains easily understandable questions for children (119). There are questions in connection with physical fitness, general well-being, emotional state, and social life.

Previous studies showed lower HRQoL in patients with pediatric IBD compared to healthy controls, also increased HRQoL in patients after one year of diagnosis (120–123). Hill et al. found that patients receiving EEN had the worst HRQoL, while patients receiving anti-TNF therapy had better HRQoL compared to patients on immunomodulator and/or steroid therapy (122). Different studies showed an association between activity indices and HRQoL (122,124).

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2. OBJECTIVES

The primary aim of investigations was to collect data on 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 joint involvement.
b. The secondary aim was to analyze the association of joint involvement with disease activity and HRQoL.

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3. PATIENTS AND METHODS

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

3.1.1. 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 between September 2016 and April 2018. Healthy controls were also included.

3.1.2. Subjects

3.1.2.1. 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 (1). Patients were treated according to the ESPGHAN guidelines (33,35).

3.1.2.2. 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). The remaining 191 (mean age: 14.8 ± 1.9 years, 91 (47.1%) male) were measured in 2017 in a local secondary school (healthy control group B) with the same device (125).

3.1.3. Methods

3.1.3.1. Anthropometric parameters and body composition

Height was measured by trained staff using a validated fixed stadiometer. Weight and BC were measured using the same multi-frequency (MF) bioelectrical impedance analyzer (InBody 720 (Biospace Co, Ltd, Seoul, Korea)) both in healthy children and patients. The technical validity of the analyzer has been confirmed previously in adults and children as well (126,127).

The InBody 720 uses eight tactile electrodes to measure segmental impedances at the four limbs and trunk using a 250mA alternating electrical current at multifrequency of 1, 5, 50, 250, 500, and 1000 kHz, altogether 30 impedance measurements in each of the five segments. The test-retest reliability of the device is >99% (128). The device provides quantitative values about TBW, FFM, SMM, and body fat mass (BFM). Measurements were performed before noon (8.00-12.00), after at least two hours of fasting in minimal clothing, without jewelry and watches, with abducted upper (30°) extremities, according to the manufacturer's instructions (129).

3.1.3.2. Other patients-related parameters

Disease activity was evaluated by the Paediatric Crohn's disease Activity Index (PCDAI) and Paediatric Ulcerative Colitis Activity Index (PUCAI) scores (30,32). Further disease-specific information (e.g. laboratory parameters, disease location, medications) was collected from the medical records of the patients within 7 days of BC analysis.

3.1.4. Data analysis and statistics

The Shapiro-Wilks test and normal probability plot analysis were used to determine whether the data were normally distributed. Data were presented as mean and standard deviation (SD), unless indicated otherwise. Height, weight, and BMI values were converted to age- and sex-specific standard deviation Z scores according to the Hungarian standard reference data from Kalman Joubert (92). 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. The maximum interindividual difference allowed within a pair was <1 year in age and 1 kg/m2 in BMI.

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 (130). 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. With the following equation, L, M, and S values can help to create percentiles (C_α) (1):

$C_\alpha(t) = M(t) \times [1+L(t) \times S(t) \times z_\alpha]^{1/L(t)}$ (1)

where M(t), L(t), S(t), and $C_\alpha(t)$ indicate the corresponding values of each parameter at a given age, sex or BMI (t). z_α is the normal equivalent deviation corresponding to the centile (eg, α=50, z_α=0; α=75, z_α= 0.674; α=90, z_α=1.282; α=95, z_α=1.645; and α=97, z_α=1.881).

After rearranging of equation 1, an individual child's specific BC parameter's Z score (e.g. FFM, TBW, SMM or BFM) can be converted to the following SDS:

Z ie, $SDS=\{[Y/M(t)]^{L(t)}-1\}/[L(t) \times S(t)]$ (2)

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 (131).

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).

3.1.5. Ethics

The study was approved by the Semmelweis University's Institutional Committee for Research Ethics (SE TUKEB No: 215/2016) and (OTKA 071730 approval, National Scientific Research Fund, participating authors: GSR, OC). It was performed following

the Declaration of Helsinki. All patient and their parent agreed with the study, and parents signed the parental informed consent.

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

3.2.1. Study design

Patients with IBD starting anti-TNF therapy (ADA or IFX) were consecutively involved in this single center, 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 laboratory parameters were assessed at initiation of anti-TNF therapy (measurement 0, M0), at the end of induction (M2), and at 6 months (M6) in patients with CD and UC.

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 ≤-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.

3.2.2. Subjects

All in all 32 patients with IBD, 21 with CD (age: 15.2±2.6 years (mean+SD), 9 (42%) male), and 11 with UC (age: 16.4±2.2 years, 5 (45%) male) were consecutively recruited in this study. Diagnosis for IBD was made according to the Porto criteria (1). Patients received treatment determined by the ESPGHAN guidelines (33,35). For assessing disease activity, the PCDAI and PUCAI scores were used in CD and UC patients, respectively (30,32). 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 (e.g., diabetes mellitus), known active malignancy, fracture. Patients, who had to stop anti-TNF therapy were also excluded (hypersensitivity to IFX, surgery, or other reasons). Anti-TNF therapy was indicated based on the administration criteria of the National Health Insurance Fund of Hungary and international guidelines (33,35).

3.2.3. Methods

3.2.3.1. Anthropometric parameters and body composition

Height, weight, and BC parameters were measured with the same device and instructions as in the study discussed in Chapter 3.1. Height, weight, and BMI Z scores were calculated based on the Hungarian reference charts from Kalman Joubert (92). BC parameters were analyzed using BMI based Z scores, created from the healthy population according to Chapter 3.1.4.

3.2.3.2. 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) (132). The questionnaire was completed by patients on the day of BC measurement, at each measurement point. 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. The questionnaire in Hungarian is in Appendix 1.

3.2.3.3. Assessment of health-related quality of life

For assessing HRQoL, the disease-specific Canadian IMPACT-III Quality of Life questionnaire was used, which was adapted to Hungarian by Szabó et al (133,134). 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. The questionnaire in Hungarian is in Appendix 2.

3.2.3.4. Other patient-related parameters

Disease location, laboratory parameters, concomitant medical therapy, and disease activity index were obtained from medical records at the time of BC, PA, and HRQoL evaluation. The localization of the disease was determined by the Paris classification.

3.2.4. Statistical analysis

Continuous variables are shown as means ± SD on figures and in tables. To compare continuous variables with parametric distribution, an independent t-test was applied. 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). Non-parametric variables, like results of PA and HRQoL 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).

3.2.5. Ethics

This study was also approved by Semmelweis University's Institutional Committee for Research Ethics (SE TUKEB No: 215/2016). Parental informed consent was mandatory for inclusion in the study.

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

3.3.1. 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 (Beata 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.

3.3.2. Subjects

Eighty-two patients (age: 13.7 ± 3.2 years (mean±SD), male:female 1.2:1) with CD were involved. All patients with signed parental informed consent were included in the study. Like in the previous studies, the diagnosis of IBD was established according to the Porto criteria (1), and patients were treated based on the ESPGHAN guidelines (33,35).

3.3.3. Methods

3.3.3.1. 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 focused on 73 joints limited to 7 bilateral enthuses, according to the Spondyloarthritis Research Consortium of Canada Enthesitis Index (135). 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. Enthesitis was defined as tenderness by palpation with or without swelling. 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.

3.3.3.2. 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).

3.3.3.3. Patient-related parameters

Laboratory parameters, PCDAI, and medications were collected from the medical records of the patients. The inactive disease was defined as a PCDAI score of <10 points, a PCDAI between 10 and 30 referred to mild disease, and if the PCDAI score is ≥30 we reported an active disease (31).

3.3.4. Statistical analysis

Normal distribution was determined with the Kolmogorov-Smirnov test. Descriptive measures (medians, means, ranges, and SE) were determined as continuous variables (i.e., age, sex, and clinical disease activity indices such as laboratory parameters, use of medication, and scores of disease activity indices). Frequencies were handled as categorical variables (i.e., different types of joint involvement), along with 95% confidence intervals (CIs) for means and proportions. 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 association between clinical disease activity indices (PCDAI, CRP, thrombocytes, IMPACT-III; all continuous variables), and joint involvement such as arthritis, joint contractions and arthralgia and biological therapy (as a categorical variable). 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).

3.3.5. Ethics

The study was approved by the Medical Research Council Scientific and Research Ethics Committee. All parent(s)/caregiver(s) and patients older than 7 years of age signed the informed consent.

4. RESULTS

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

4.1.1. Anthropometric and body composition parameters of healthy control population and patients with inflammatory bowel disease

4.1.1.1. Healthy control populations

For creating a reference population, the BC results of two healthy control groups were merged. Comparing these groups, we did not find a difference between height, weight, or BMI Z scores, however, patients in healthy control group A were older, which was considered not to be a contraindication of merging (Table 1.).

Table 1. Anthropometric data of healthy control groups

Variables	Healthy control group A	Healthy control group B
n	116	191
Age (years)	13.4 ± 2.2	14.8 ± 1.9*
Sex (males (%))	53 (45.7%)	91 (48%)
Height Z score	0.4±0.9	0.5±1.1
Weight Z score	0.0±0.7	0.0±0.9
BMI Z score	-0.1±0.8	-0.2±0.8

Data are shown as mean ± SD. Abbreviations: SD: standard deviation, *: vs. Healthy control group A, $p<0.05$

Descriptive statistics of the final healthy population according to age groups are shown in Table 2/a and b.

4.1.1.2. Patients with inflammatory bowel disease

In the IBD group, 31 patients had CD (mean age: 14.1±2.5 years, 19 males), from which 20 (65%) were newly diagnosed and 11 (35%) were starting anti-TNF therapy. Twenty-six patients had UC (mean age: 14.2±2.9 years, 13 males), among them 14 (54%) were newly diagnosed and 12 (46%) started anti-TNF treatment. There was no significant difference between age, anthropometrics, or BC parameters. Most of the CD patients had mild disease (15/31 (48%)), while most of the patients with UC (12/26 (46%)) had moderate disease activity. Patients with CD had a significantly higher CRP and

thrombocyte level, and lower hemoglobin and albumin level compared to the UC group. According to disease location, most of the patients with CD had ileocolonic disease (15/31 (48.4%)), in addition, a lot of patients had upper GI involvement as well (16/31 (51.6%). Most of the patients with UC had left-sided colitis 12/26 (46%). Based on disease behavior, the majority of patients with CD a non-stricturing non-penetrating disease (25/31 (80%)). Four out of 31 (13%) and ten out of 26 (38%) patients received systemic glucocorticoids in CD and UC groups, respectively. Further clinical characteristics, anthropometrics, activity indices, laboratory parameters, disease location, and medical treatment are summarized in Table 3/a and b.

Table 2/a. Descriptive statistics of healthy controls according to age groups

Age groups	**9.9 to 10.9**	**11 to11.9**	**11.9 to 12.9**	**12.9 to 13.9**	**14.0 to 14.9**
n	20	34	31	54	38
Sex (males (%)	9 (45%)	18 (52.9%)	11 (35.5%)	28 (51.8%)	18 (47.4%)
Age (years)	10.5±0.3	11.5±0.3	12.5±0.3	13.4±0.3	14.6±0.2
Height (cm)	143.8±5.1	151.1±8.2	157.6±7.8	163.1±7.8	169.6±7.7
Height Z score	0.3±0.9	0.4±1.1	0.4±1.1	0.5±1	0.6±1
Weight (kg)	36.4±6.3	41.7±8.1	44.8±8.3	49.6±8.5	56.8±9.4
Weight Z score	0.1±0.8	0.1±0.8	-0.1±0.8	-0.1±0.8	0.1±0.8
BMI (kg/m^2)	17.5±2.5	18.1±2.4	17.9±2.3	18.6±2.5	19.7±2.5
BMI Z score	-0.1±0.8	-0.1±0.7	-0.4±0.7	-0.4±0.7	-0.2±0.7
TBW (l)	21.3±2.5	24.5±3.9	27.1±3.9	30.6±4.6	35±5.6
FFM (kg)	29.3±3.4	33.7±5.3	36.9±5.3	41.8±6.2	47.9±7.6
SMM (kg)	15.8±2	18.3±3	20±3.4	23.2±3.7	26.7±4.5
BFM (kg)	7.3±3.9	8.6±5.1	7.8±4.4	8.6±7.5	8.9±5.4

Data are shown as mean ± SD. Age groups are shown as min to max age in years. Abbreviations: SD- standard deviation; BMI - body mass index; TBW - total body water; FFM - fat free mass; BFM - body fat mass; SMM - skeletal muscle mass

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Table 2/b. Descriptive statistics of helathy controls according to age groups

Age groups	**14.9 to 15.9**	**15.9 to 16.9**	**16.9 to 17.9**	**18 to 19.3**
n	54	46	21	9
Sex (males (%)	30 (55.5%)	19 (41.3%)	5 (23.8%)	5 (55.5%)
Age (years)	15.5±0.3	16.4±0.3	17.3±0.3	18.5±0.5
Height (cm)	170.5±7.3	171.9±8.5	170.9±10.1	174.7±7.9
Height Z score	0.3±1	0.4±1	0.3±1.2	0.7±0.7
Weight (kg)	60.4±10.5	62.3±9.9	60.8±11.1	63.2±8.9
Weight Z score	0.1±1	0.1±0.8	-0.1±0.9	0.3±0.8
BMI (kg/m2)	20.7±2.7	21±2.3	20.7±2.6	20.6±1.3
BMI Z score	0±0.8	-0.1±0.7	-0.2±0.8	0.2±0.8
TBW (l)	36.3±6.2	37.1±7.6	35.8±7.8	39.4±8
FFM (kg)	48.6±10.5	50.9±10.4	49±10.6	53.8±10.8
SMM (kg)	27.8±5.4	28.6±6.5	27.4±6.4	30.4±6.6
BFM (kg)	10.8±6.7	11.3±4.6	11.8±4.9	9.4±3.8

Data are shown as mean ± SD, unless indicated otherwise. Age groups are shown as min to max age in years. Abbreviations: SD: standard deviation; BMI: body mass index; TBW: total body water; FFM: fat free mass; BFM: body fat mass; SMM: skeletal muscle mass

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Table 3/a. Clinical, anthropometric data, and activity index of patients with inflammatory bowel disease

Variables	Inflammatory bowel disease	Crohn's disease	Ulcerative colitis
Number of patients	57	31	26
Age in years	14.2 ± 2.7	14.1 ± 2.5	14.2 ± 2.9
Sex, males n (%)	32 (56)	19 (61)	13 (50)
Numer of newly diagnosed patients n (%)	34 (59)	20 (64)	14 (54)
Anthropometric and body composition parameters			
Height (cm)	161.9 ± 14.4	160.7 ± 12.5	163.5 ± 16.4
Height Z score	0.3 ± 1.1	0.1 ± 1.1	0.44 ± 1.2
Weight (kg)	46.9 ± 12.0	45.6 ± 11.2	48.4 ± 13.2
Weight Z score	-0.5 ± 0.9	-0.5 ± 1.0	-0.4 ± 0.9
BMI (kg/m2)	17.6 ±2.7	17.5 ± 2.8	17.8 ± 2.7
BMI Z score	-0.7 ± 0.8	-0.7 ± 0.9	-0.7 ± 0.7
SMM (kg)	22.3 ± 8.4	23.1 ± 9.8	21.4 ± 6.2
FFM (kg)	37.9 ± 9.7	36.6 ± 8.7	39.6 ± 10.8
TBW (l)	27.8 ± 7.2	26.9 ± 6.4	29.0 ± 8.0
BFM (kg)	8.5 ± 5.3	8.3 ± 5.0	8.9 ± 5.7
Disease activity index			
PCDAI/PUCAI (CI)		22.3 ± 14.8	35.6 ± 20.8
PCDAI ≤10 n (%)		8 (25)	
PCDAI 11-29 n (%)		15 (48)	
PCDAI 30-39 n (%)		4 (12)	
PCDAI ≥40 n (%)		4 (12)	
PUCAI < 10 n (%)			3 (11)
PUCAI 10-34 n (%)			8 (30)
PUCAI 35-64 n (%)			12 (46)
PUCAI 65< n (%)			3 (11)

Data are shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation; BMI: body mass index; TBW: total body water; FFM: fat free mass; BFM: body fat mass; SMM: skeletal muscle mass. PCDAI: pediatric Crohn's disease activity index. PUCAI: pediatric ulcerative colitis activity index

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Table 3/b. Laboratory data, disease location and medical treatment of patients with inflammatory bowel disease

Variables	**Inflammatory bowel disease**	**Crohn's disease**	**Ulcerative colitis**
Laboratory parameters			
CRP (mg/l)	20.43 ± 29.5	30.4 ± 32.6	8.1 ± 19.2**
Haemoglobin (g/dL)	120.1 ± 15.9	116.2 ± 150.9	125.0 ± 16.5*
Thrombocytes (G/L)	414.4 ± 171.2	472 ± 150.9	343.0 ± 170.6**
Albumin (g/L)	41.4 ± 5.0	39.4 ± 5.0	43.1 ± 4.3 **
Extent / Location of the disease and disease behavior			
L1 Ileal n (%)		9 (29)	
L2 Colonic n (%)		7 (22.5)	
L3 Ileocolonic n (%)		15 (48.4)	
L4 Upper gastrointestinal tract n (%)		16 (51.6)	
E1 Proctitis n (%)			1 (3.8)
E2 Left-sided n (%)			12 (46)
E3 Extensive n (%)			2 (7.7)
E4 Pancolitis n (%)			11 (42.3)
B1 Non-stricturing, non-penetrating n (%)		25 (80)	
B2 Stricturing n (%)		5 (16)	
B3 Penetrating n (%)		1 (3.2)	
S0 Never severe n (%)			16 (61)
S1 Ever severe n (%)			10 (38)
Medical treatment n (%)			
5-aminosalicylic acid n (%)	42 (73)	18 (58)	23 (88)
Azathioprine n (%)	37 (65)	24 (77)	12 (46)
Methotrexate n (%)	1 (0.02)	0	1 (0.04)
Antibiotics n (%)	10 (17)	8 (25)	2 (0.07)
Systemic glucocorticoid n (%)	15 (27)	4 (13)	10 (38)
Topical steroid n (%)	6 (10.5)	4 (13)	1 (0.04)
Exlusive enteral nutrition n (%)	16 (28)	16 (51)	0
Adalimumab n (%)	17 (29.8)	8 (25.8)	9 (34)
Infliximab n (%)	5 (8)	3 (9)	2 (0.7)

Data are shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation; *: vs. Crohn's disease, p<0.05; ** : vs. Crohn's disease, p< 0.005

4.1.2. 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 and BMI (in absolute values and Z scores also) than that of non-adjusted healthy children. SMM and FFM were lower in patients, meanwhile, BFM did not differ between these groups. Baseline characteristics of the normal and IBD patients' population are summarized in Table 4.

Table 4. Baseline characteristics of the healthy population and patients with inflammatory bowel disease

Variables	Healthy controls	Inflammatory bowel disease
n	307	57
Age (years)	14.3±2.1	14.2±2.7
Sex (males n (%))	143 (47)	32 (56)
Height (cm)	164.2±11.7	162±14.4
Height Z score	0.4±1	0.3±1.1
Weight (kg)	53.2±12.5	46.9±12*
Weight Z score	0±0.8	-0.5±1*
BMI (kg/m^2)	19.5±2.7	17.6±2.8*
BMI Z score	-0.2±0.8	-0.7±0.9*
TBW (l)	32.1±7.7	27.9±7.3*
FFM (kg)	43.8±10.7	38±9.8*
SMM (kg)	24.4±6.3	22.3±8.4*
BFM (kg)	9.5±5.8	8.6 ± 5.3

Data are shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standars deviation; BMI: body mass index; TBW: total body water; FFM: fat free mass; SMM: skeletal muscle mass; BFM: body fat mass; *: vs. Healthy controls, p<0.05

4.1.3. 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).

4.1.4. Development of BMI Z score based body composition Z scores

Based on these, a propensity score matched control population was created (Table 5). 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 SMM Z score calculation was implemented. Z scores and percentiles were calculated for TBW, FFM and BFM as well.

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Table 5. Patients with inflammatory bowel disease vs. controls after adjustment by age, sex, and BMI

Variables	Patients with inflammatory bowel disease	Adjusted controls
n	57	55
Age (years)	14.1± 2.7	14.4 ± 2.3
Sex (males n (%))	32 (56)	32 (58)
Height (cm)	161.9 ± 14.4	165.5 ± 12.7
BMI (kg/m2)	17.6 ± 2.7	17.9 ± 2.5
Height Z score	0.3 ± 1.1	0.5 ± 1.0
Weight Z score	-0.5 ±0.9	-0.4 ± 0.8
BMI Z score	-0.7 ± 0.8	-0.7 ± 0.8
TBW (l)	27.9 ± 7.3	31.1 ±7.7*
FFM (kg)	37.9 ± 9.8	42.5 ±10.5*
SMM (kg)	22.3 ± 8.4	23.4 ±6.2
BFM (kg)	8.6 ± 5.3	7.2 ± 4.5

Data are shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation; BMI - body mass index; TBW - total body water; FFM - fat free mass; BFM - body fat mass; SMM - skeletal muscle mass; *vs. Patients $p<0.05$

BMI Z score based LMS values were determined, and percentile boundaries were calculated and plotted by normalizing to age, sex and BMI. (Figure 2/a-h, Table 6/a-d.). An individual child's SMM Z score value was calculated according to the equation above in the statistics section. BMI based Z scores for FFM and BFM were also created, according to the same method.

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Table 6/a. LMS values and specific percentile limit for skeletal muscle mass according to BMI Z scores

BMI Z score	L	M	S	5th	10th	25th	50th	75th	90th	95th
-1.99	0.8	19.8	0.2	13.9	15.1	17.3	19.8	22.4	24.8	26.2
-1	0.6	20.9	0.2	14.2	15.6	18.0	20.9	24.0	26.9	28.7
0	0.2	24.8	0.2	16.5	18.1	21.1	24.8	29.1	33.5	36.3
1	0.1	27.0	0.3	17.5	19.3	22.6	27.0	32.0	37.3	40.8
1.99	0.2	29.2	0.3	18.6	20.6	24.4	29.2	34.7	40.3	43.9

Abbreviations: L - skewness; M – median; S coefficient of variation.

Table 6/b. LMS values and specific percentile limit for total body water according to BMI Z scores

BMI Z score	L	M	S	5th	10th	25th	50th	75th	90th	95th
-1.99	0.4	26.8	0.2	19.1	20.7	23.5	26.8	30.5	34.0	36.2
-1	0.5	28.0	0.2	19.4	21.2	24.3	28.0	31.9	35.7	38.1
0	0.2	32.6	0.2	22.2	24.2	28.0	32.6	37.8	43.1	46.4
1	0.2	35.3	0.2	23.7	26.0	30.1	35.3	41.2	47.2	51.1
1.99	0.4	38.0	0.2	25.4	27.9	32.5	38.0	44.1	50.0	53.8

Abbreviations: L - skewness; M – median; S coefficient of variation.

Table 6/c. LMS values and specific percentile limit for fat free mass according to BMI Z scores

BMI Z score	L	M	S	5th	10th	25th	50th	75th	90th	95th
-1.99	0.5	38.2	0.2	26.7	29.1	33.3	38.2	43.5	48.6	51.7
-1	0.2	44.7	0.2	30.5	33.3	38.3	44.7	51.8	58.9	63.5
0	0.1	48.2	0.2	32.4	35.4	41.0	48.2	56.4	64.7	70.2
1	0.3	51.9	0.2	34.6	38.0	44.2	51.9	60.5	69.0	74.5
1.99	0.5	38.2	0.2	26.7	29.1	33.3	38.2	43.5	48.6	51.7

Abbreviations: L - skeweness; M – median; S coefficient of variation.

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Table 6/d. LMS values and specific percentile limit for body fat mass according to BMI Z scores

BMI Z score	L	M	S	5th	10th	25th	50th	75th	90th	95th
-1.99	-0.1	2.5	0.6	0.9	1.1	1.6	2.5	3.7	5.5	7.0
-1	0.3	5.2	0.5	1.9	2.5	3.6	5.2	7.2	9.6	11.2
0	0.5	9.2	0.4	4.1	5.0	6.8	9.2	12.0	14.8	16.6
1	0.8	15.2	0.3	7.9	9.4	12.1	15.2	18.4	21.3	23.1
1.99	1.2	22.6	0.2	14.5	16.4	19.4	22.6	25.7	28.4	30.0

Abbreviations: L - skeweness; M – median; S coefficient of variation.

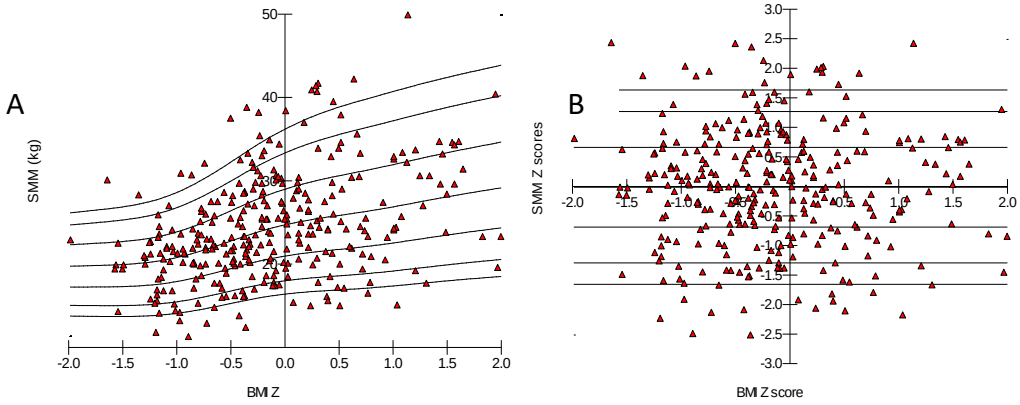

Figure 2/A. Skeletal muscle mass percentiles according to BMI Z scores in healthy controls

Figure 2/B. Skeletal muscle mass Z score percentiles according to BMI Z scores in healthy controls

Abbreviations: SMM: skeletal muscle mass, BMI: body mass index. Triangles show each child from the control population.

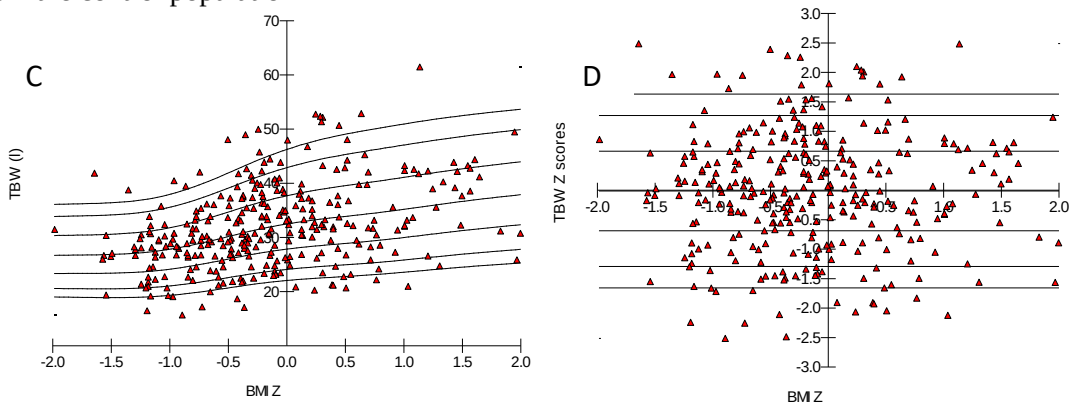

Figure 2/C. Total body water percentiles according to BMI Z scores in healthy controls

Figure 2/D. Total body water Z score percentiles according to BMI Z scores in healthy controls

Abbreviations: TBW: total body water, BMI: body mass index. Triangles show each child from the control population.

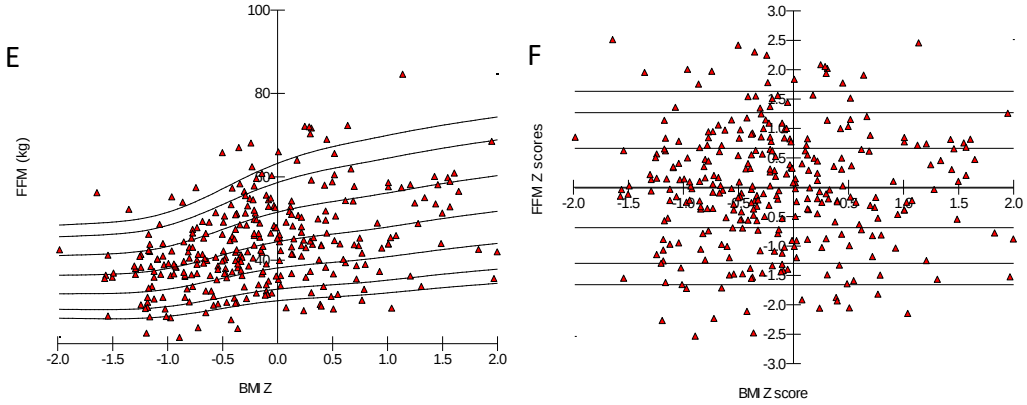

Figure 2/E. Fat free mass percentiles according to BMI Z scores in healthy controls

Figure 2/F. Fat free mass Z score percentiles according to BMI Z scores in healthy controls

Abbreviations: FFM: fat free mass, BMI: body mass index. Triangles show each child from the control population

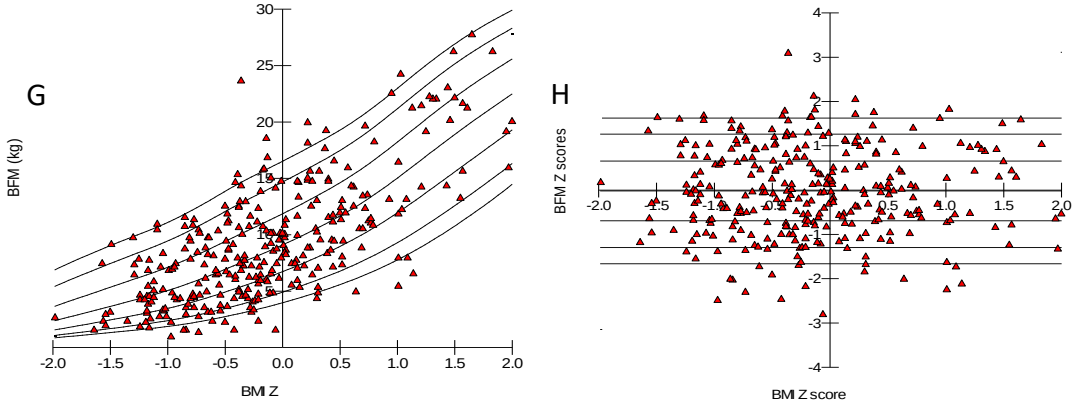

Figure 2/G. Body fat mass percentiles percentiles according to BMI Z scores in healthy controls

Figure 2/H. Body fat mass Z score percentiles percentiles according to BMI Z scores in healthy controls

Abbreviations: BFM: body fat mass, BMI: body mass index. Triangles show each child from the control population

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

Despite the different laboratory parameters between CD and UC group (Table 3/a), there was no significant difference in terms of body size and BC parameters (Table 7.).

Table 7. Anthropometric and body composition data of patients with inflammatory bowel disease

Variables	Inflammatory bowel disease	Crohn's disease	Ulcerative colitis
Number of patients	57	31	26
Age (years)	14.2 ± 2.7	14.1 ± 2.5	14.2 ± 2.9
Sex (males n (%))	32 (56)	19 (61)	13 (50)
Height Z score	0.3 ± 1.1	0.1 ± 1.1	0.44 ± 1.2
Weight Z score	-0.5 ± 0.9	-0.5 ± 1.0	-0.4 ± 0.9
BMI Z score	-0.7 ± 0.8	-0.7 ± 0.9	-0.7 ± 0.7
TBW Z score	-0.3 ± 1.2	-0.5 ± 1.1	-0.1 ± 1.4
FFM Z score	-0.3 ± 1.2	-0.5 ± 1.1	-0.1 ± 1.4
SMM Z score	-0.0 ± 1.8	0.1 ± 2.1	-0.2 ±1.4
BFM Z score	0.4 ± 1.3	0.3 ± 1.4	0.5 ± 1.2

Data are shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation; BMI: body mass index; TBW: total body water; FFM: fat free mass; BFM: body fat mass; SMM: skeletal muscle mass

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

4.2.1. Baseline clinical and demographic characteristics

During the study period, thirty-five patients started biological therapy at the 1st Department of Pediatrics, from which three could not participate in the study due to autism spectrum disorder (n=1), young age (younger than 10 years) (n=1), and leg fracture (n=1) (Figure 2). Altogether, 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 enrolled. Other patients were lost because of changing the attending physician, moving, and transitioning to adult care, or bad compliance to the study (skipping study visits). Anti-TNF therapy (ADA or IFX) was administered according to the standard dosing protocols. During the study period, four patients needed intensification based on clinical judgement (Figure 3.) (136).

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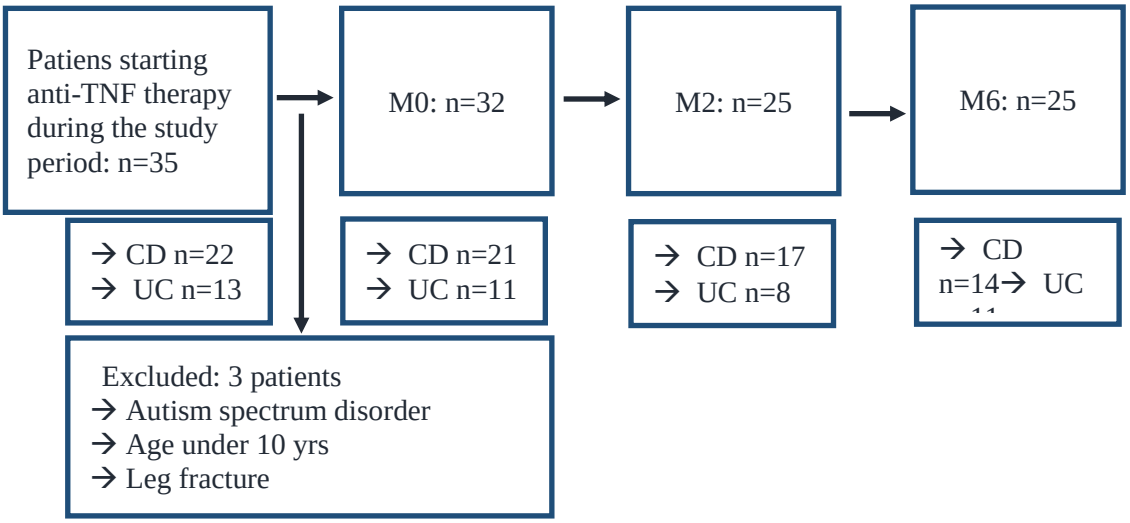

Figure 3. Patient number at each study visit - flow chart

Abbreviations: CD: Crohn's disease; UC: ulcerative colitis; M0: measurement at the beginning of the study; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy (136)

Patients with CD had significantly lower hemoglobin and higher thrombocyte level compared to patients with UC. The median time between diagnosis and initiating anti-TNF therapy was 1.4 and 3 years in CD and UC groups, respectively. The disease location was mostly ileocolonic (42.8%) or colonic (33.3%) in CD. Most of the patients with UC had a left sided disease (81.8%). Concomitant therapy was AZA in 80% and 63% of patients with CD and UC, respectively. Nineteen percent of CD and 36% of UC patients received systemic steroids. Further data on baseline demographics, clinical characteristics, laboratory markers, and therapy are summarized in Table 8 (136).

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Table 8. Baseline demographic and clinical characteristics of patients with Crohn's disease and ulcerative colitis

Variables	Crohn's disease	Ulcerative colitis
Number of patients	21	11
Age (years)	15.2±2.6	16.4±2.2
Gender,male, n (%)	9 (42)	5 (45)
Median time between diagnosis and starting anti-TNF therapy (year (IQR))	1.4 (3.6)	3.0 (3.3)
PCDAI/PUCAI	23.1±14.0	27.3±23.0
CRP (mg/L)	30.8±43.8	14.1±29.3
Haemoglobin (g/dL)	114.0±19.8	129.6±16.6*
Thrombocytes (G/L)	451.0±169.4	285.3±120.9**
Albumin (g/L)	38.6±5.8	42.4±7.7
Extent / Location of the disease according to Paris Classification		
L1 Ileal n (%)	5 (23.8)	
L2 Colonic n (%)	7 (33.3)	
L3 Ileocolonic n (%)	9 (42.8)	
L4 Upper gastrointestinal tract n (%)	15 (71.4)	
E1 Proctitis n (%)		0
E2 Left-sided n (%)		9 (81.8)
E3 Extensive n (%)		0
E4 Pancolitis n (%)		2 (18.2)
Disease Behaviour (B1. B2. B3)		
B1 Non-stricturing, non-penetrating n (%)	14 (66)	
B2 Stricturing n (%)	5 (24)	
B3 Penetrating n (%)	2 (9)	
Medical treatment n (%)		
5-ASA n (%)	14 (66)	10 (90)
Azathioprine n (%)	17 (80)	7 (63)
Methotrexate n (%)	0	1 (9)
Antibiotics n (%)	9 (42)	3 (27)
Systemic corticosteroid n (%)	4 (19)	4 (36)
Topical steroid	3 (14)	3 (27)

Data re shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index; CRP: C-reactive protein. *: vs. Crohn's disease, $p < 0.05$; **:vs. Crohn's disease, $p < 0.005$ (136)

58% of the patients with CD (10/17) and 37.5% of the patients with UC (3/8) achieved clinical remission by the end of the induction period (M2). One CD patient and one UC patient showed a response to anti-TNF therapy without achieving clinical remission, based on disease activity indices. After six months of anti-TNF therapy seventy-eight percent of the children with CD (11/14) and fifty-four percent of the patients with UC (6/11) were in remission.

4.2.2. 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) (Table 9) (136).

Table 9. Baseline body composition parameters of patients with Crohn's disease and ulcerative colitis

Variables	Crohn's disease	Ulcerative colitis
Height Z score	-0.2±1.2	0.6±1.1
Weight Z score	-1.0±0.8	-0.6±0.7
BMI Z score	-1.1±0.7	-0.9±0.7
FFM Z score	-0.4±1.1	0.5±1.3*
SMM Z score	-0.5±1.1	0.4±1.3
BFM Z score	1.0±1.2	1.0±1.3

Data are shown as mean ± SD. Abbreviations: SD: standard deviation; BMI: body mass index; FFM: fat free mass; SMM: skeletal muscle mass; BFM: body fat mass, * vs. Crohn's disease, $p<0.05$ (136)

4.2.3. 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) (Figure 4/A and B. (136)).

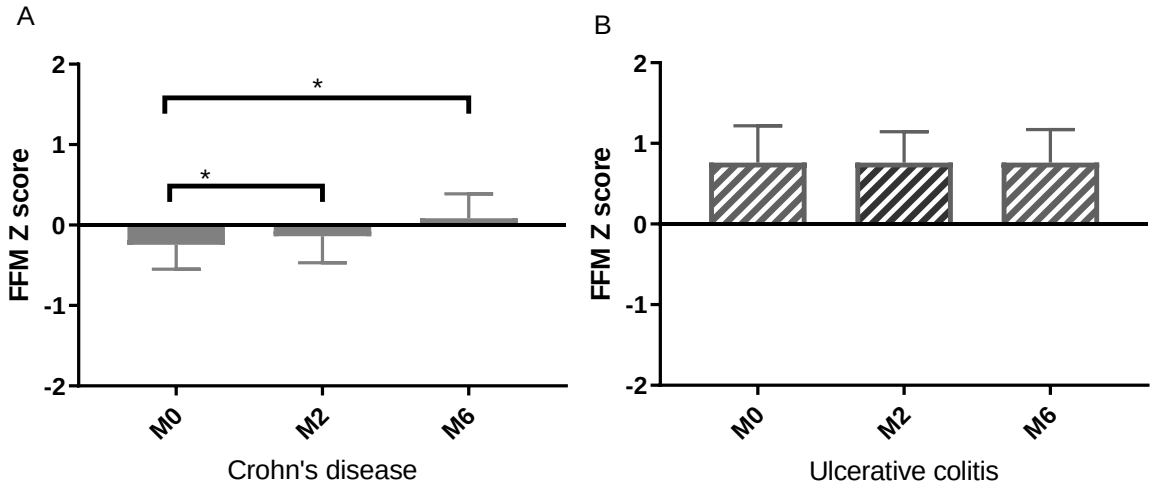

Figure 4/A and B. Fat free mass Z score changes in patients with Crohn's disease and ulcerative colitis

Data are shown as mean ± SD. Abbreviations: M0: measurement at the beginning of anti-TNF therapy; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy; *: vs. M0, $p<0.05$ (136)

4.2.4. 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 (Table 10. (136)).

Table 10. Health-related quality of life and physical activity in patients with Crohn's disease and ulcerative colitis during the study period

Variables	Crohn's disease (n=21)			Ulcerative colitis (n=11)		
	M0	M2	M6	M0	M2	M6
IMPACT-III (35-175)	128.5 (111.5; 137.8)	137.5 (125.3; 146.3)	144 (126.8; 154.5)	109 (83;129)	116 (94;140)	116 (95;145)
PAQ (1-5)	1.1 (1.0;1.8)	1.5 (1.0;2.3)	2.3 (1.5;2.4)	1.6 (1.0;2.5)	2.15 (1.6;2.4)	1.8 (1.0;2.0)

Data are shown as median (pc 25;75). PAQ: physical activity questionnaire; M0: measurement at the beginning of anti-TNF therapy; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy (136)

4.2.5. 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 by M6 PA level of patients was comparable to the PA of matched controls (2.3 vs. 2.4). PA among patients with UC did not differ from PA of controls, and it remained the same throughout the study period (M0: 1.6 vs. 2.3. M6: 1.8 vs. 2.2) (Table 10 and Figure 5/A and B (136)). In patients with CD, IMPACT III and PAQ scores showed a correlation at baseline (r=0.73, p=0.007).

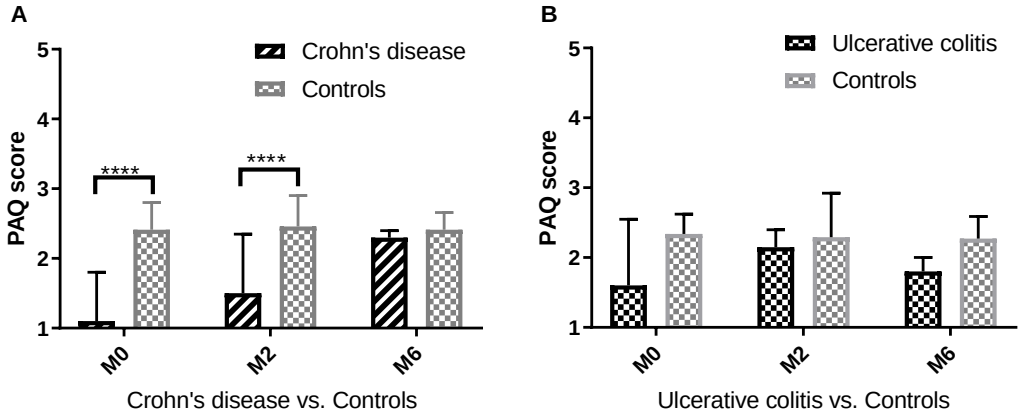

Figure 5/A and B. Physical activity of patients with Crohn's disease compared to age, sex and BMI Z score adjusted controls

Data are shown as median (pc 25;75). Abbreviations: PAQ: physical activity questionnaire, M0: measurement at the beginning of anti-TNF therapy; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy ****: vs. Crohn's disease, p<0.00005 (136)

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4.2.6. Comparison of children with or without risk of sarcopenia

According to the baseline SMM Z score, patients were also divided into two groups (Table 11). 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 (Table 11.). 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 hange in Group NS (Figure 6., Table 12) (136).

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Table 11. Patients with skeletal muscle mass score ≤ -1 (Group RS) compared to patients > -1 SMM Z score (Group NS)

Variables	**Group RS**	**Group NS**
Number of patients	10	22
Age in years	13.9±2.8*	16.4±1.9
Gender male n (%)	20% (2/10)	54.5% (12/22)
CD patients n (%)	8 (80)	13 (59)
PCDAI	25.9±16.3	21.4±12.8
PUCAI	17.5±3.5	29.4±25
Mean disease duration (year) [IQR]	3.0 [4.9]	2.7 [2.5]
Laboratory data		
CRP (mg/L)	36.2±60.4	19.8±24.6
Haemoglobin. (g/dL)	115.3±24.9	121.1±17.4
Thrombocytes (G/L)	379.6±100.7	403.8±200.6
Albumin (g/L)	39.0±7.9	40.3±6.0
Extent / Location of the disease		
L1 (Ileal) n (%)	2 (20)	3 (13.6)
L2 (Colonic) n (%)	2 (20)	5 (22.7)
L3 (Ileocolonic) n (%)	4 (40)	5 (22.7)
L4 (Upper gastrointestinal tract) n (%)	8 (80)	8 (36)
E1 (Proctitis) n (%)	0	0
E2 (Left-sided) n (%)	2 (20)	6 (27)
E3 (Extensive) n (%)	0	1 (4.5)
E4 (Pancolitis) n (%)	0	2 (9)
Disease Behaviour (B1. B2. B3)		
B1 Non-stricturing. non-penetrating n (%)	3 (30)	11 (50)
B2 Stricturing n (%)	4 (40)	1 (4,5)
B3 Penetrating n (%)	1 (10)	1 (4,5)

Data re shown as mean ± SD, unless indicated otherwise. Abbreviations: SD: standard deviation, PCDAI: Pediatric Crohn's Disease Activity Index, PUCAI: Pediatric Ulcerative Colitis Activity Index, CRP: C-reactive protein. *: vs. group NS, $p<0.05$ (136)

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Table 12. Comparison of body composition parameters in patients with SMM Z score ≤ -1 (Group RS) and with SMM Z score > -1 (Group NS)

	Group RS			Group NS		
Variables	M0	M2	M6	M0	M2	M6
	n=10	n=7	n=6	n=22	n=18	n=19
Height Z score	-0.7±1.1	-0.8±1.3	-0.4±1.2	0.4±1.0$^{\#}$	0.4±1.0	0.4±1.1
Weight Z score	-1.2±1.1	-1.2±1.1	-0.4±1.2	-0.7±1.1	-0.5±0.6	-0.6±0.7
BMI Z score	-1.0±1.0	-1.0±1.1	-0.3±0.7	-1.0±0.6	-0.8±0.4	-0.9±0.5
FFM Z score	-1.4±0.4	-1.2±0.4	-0.8±0.4	0.5±1.0	0.6±1.0	0.6±1.1
SMM Z score	-1.4±0.4	-1.3±0.4**	-0.8±0.4*	0.4±1.0$^{\#\#\#}$	0.5±1.0$^{\#\#\#}$	0.6±1.1$^{\#\#\#}$
BFM Z score	0.9±1.2	0.9±1.1	0.7±0.8	1.1±1.1$^{\#\#\#}$	1.1±0.9$^{\#\#\#}$	1.0±1.3$^{\#\#\#}$

Data are shown as mean ± SD. Abbreviations: RS –risk of sarcopenia, NS: without risk of sarcopenia; BMI: body mass index; FFM; fat free mass; SMM; skeletal muscle mass; BFM: body fat mass; M0: measurement at the beginning of the study; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy. *: vs M0, p<0.05, $^{\#}$: vs. the equivalent parameter in group RS, $p < 0.05$, $^{\#\#\#}$:vs. the equivalent parameter in group RS, $p < 0.0005$ (136)

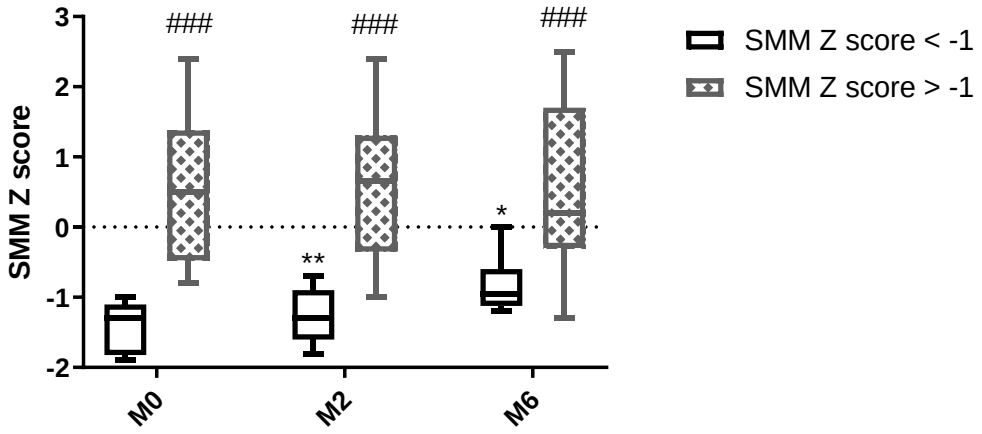

Figure 6. Changes in skeletal muscle mass Z score in children with or without risk of sarcopenia during the study period

Data are shown as mean ± SD. Abbreviations: SD: SD: standard deviation; SMM: skeletal muscle mass, M0: measurement at the beginning of the study; M2: measurement after induction therapy; M6: measurement after 6 months on anti-TNF therapy; *: vs. M0, $p < 0.05$; **:vs. M0, $p < 0.005$; ###: vs. the equivalent parameter in SMM Z score < -1, $p < 0.0005$ (136)

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

4.3.1. Clinical and demographic characteristics

Eighty-two patients were involved in this study, from which eight patients were "newly diagnosed" (diagnosis was made within 4 weeks before rheumatology assessment). Patients' demographic and clinical data are in Table 13 (137). Two patients had infantile IBD (less than 2 years at disease onset), three had very early onset IBD (2-6 years old at disease onset) and fourteen had early onset IBD (age between 6 to 10 years at disease onset). The remaining participants were 10-18 years of age.

Table 13. Demographic and clinical data of patients

Variables	Patient value/description
n	82
Sex ratio (male: female)	1.2:1
Age at the time of the study (years)	13.7 ± 3.2
Age at onset of Crohn's disease (years)	12.2 ± 3.6
Disease duration (months)	21.6 ± 21
CRP (mg/L)	11.8 ± 19.3
Thrombocytes (G/l)	422 ± 145
Medications at the time of study	
Sulfasalazine/mesalamine n (%)	70 (85)
Azathioprine n (%)	58 (70)
Methotrexate n (%)	5 (6)
Infliximab n (%)	16 (20)
Methylprednisolone n (%)	16 (20)
Budesonide n (%)	7 (9)
Non-steroidal anti-inflammatory drug n (%)	3 (4)

Data re shown as mean ± SD, unless indicated otherwise. Abbreviaions: CRP: C reactive protein

(137)

4.3.2. 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, and 5 patients had a remote history of documented active arthritis, without having a remaining restricted range of joint motions or contractions. Of the 24 patients with arthritis 1 had active enthesitis at the patellar ligament insertion at the inferior pole of the patella at the time of the examination. Eight (33%) of these 24 patients had active arthritis indicated by swollen joint(s) with or without stress pain, from which 4 patients also had a restricted range of motion or contraction in one or more other joints, suggestive

of previous or longstanding arthritis. The remaining 15 patients showed evidence of previous arthritis (these patients did not have active arthritis at the time of the examination), indicated by a severely restricted range of motion with or without deformity in one or more joints (Figure 7., Table 14.) (137).

Table 14. Distribution of joints with active or previous arthritis found by physical examination or documented in the medical chart (137)

	Condition revealed by physical examination during the current study		**Documented in patients' chart**
Joint	**Active arthritis (and/or enthesitis)**	**Restricted range of motion**	**Arthritis (and/or enthesitis)**
n	9	15	5
Shoulder n (%)	1 (11)		
Elbow n (%)	1 (11)		
Hand n (%)	1 (11)	3 (20)	
Lumbosacral n (%)	4 (44)		1 (20)
Hip n (%)	1 (11)	11 (73)	
Knee n (%)	4 (44) / 1 (11)	6 (40)	1 (20)
Ankle n (%)	1 (11)	2 (13)	3 (60)
Foot n (%)	1 (11)	1 (6.6)	2 (40)

4.3.3. Prevalence of arthralgia

Thirty-nine out of 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, 18/39 (46%) had only arthralgia, without arthritis. The distribution of arthralgia with or without morning stiffness in 18/82 patient history is shown in Table 15 (137). The most affected joints were the knee and ankles.

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Figure 7. Prevalence of joint involvement (arthritis, enthesitis, restricted range of motion) by objective measurement (physical examination or documented history). Conditions occurred as indicated in a total of 29/82 (35%) patients studied (137)

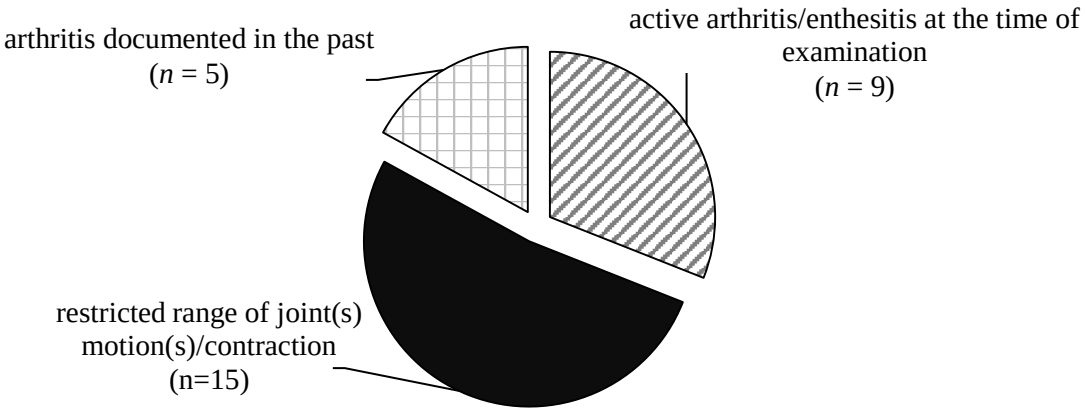


Table 15. The most frequently subjectively-affected joints (137)

Joint	**Frequency of arthralgia (without arthritis) based on history**
n	18
Shoulder n (%)	1 (5.5)
Elbow n (%)	0
Hand n (%)	0
Lumbosacral n (%)	2 (11.1)
Hip n (%)	2 (11.1)
Knee n (%)	14 (77.7)
Ankle n (%)	6 (33.3)
Foot n (%)	0

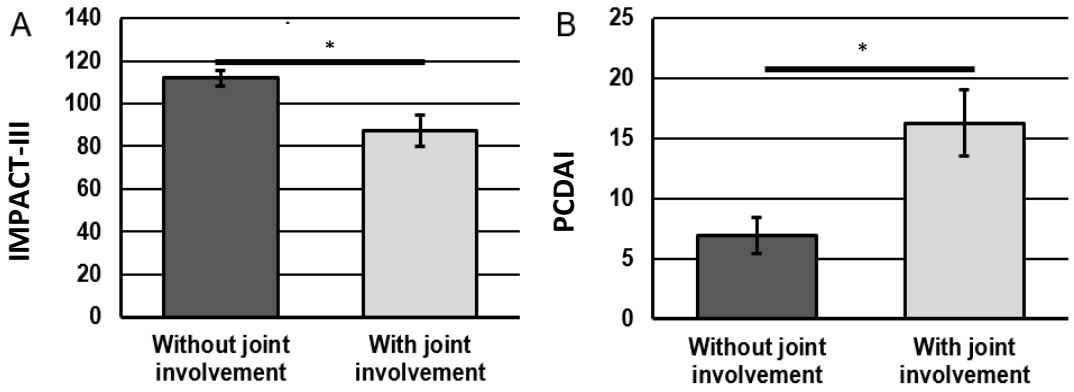
Axial involvement was present in 10/82 (12%) of the patients. One patient had sacroiliitis based on the medical records by MR imaging at diagnosis. In another three cases, patients had positive Mennell's sign at physical examination and lumbosacral pain

in history. Spondylarthritis involving the lumbosacral spine by a limited range of motion in the Schober's test was positive in one patient, and another two had morning stiffness with lower-back pain.

4.3.4. 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 (Figure 8.) (137).

Figure 8/A and B. IMPACT-III and PCDAI indices in patients with or without joint involvement (arthritis. enthesitis and/or arthralgia). (*n* = 82 patients).



Data are shown as mean± SE. Abbreviations: PCDAI: Pediatric Crohn's Disease Activity Index; *: vs with joint involvement, $p<0.05$ (137).

4.3.5. Changes in therapy based on rheumatologic evaluation

Rheumatologic examination led to changes in medication in twenty-five percent (6/24) of the patients with active arthritis at the time of examination. From these, three patients started anti-TNF therapy (IFX), two patients received non-steroidal anti-inflammatory drug and one started corticosteroids because of the joint involvement.

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5. DISCUSSION

The prevalence of IBD is increasing in the pediatric age (4). As chronic diseases, such as IBD can affect all aspect of the life of patients, including physical, social, and emotional well-being, their HRQoL, medical care, symptom control, and prognosis becomes more important day by day. As the role of malnutrition and/or sarcopenia is associated with poor prognosis, monitoring nutritional status became part of the routine follow-up protocols (45–47). However, growing evidence suggests that BMI, which was used earlier to assess nutritional status, is not sensitive enough, so different techniques have spread for the assessment of BC (138). Still, there is no gold standard method for BC measurement in pediatric patients, as every method has its pros and cons. BIA is an inexpensive, easy-to-use, non-invasive, quick method for BC measurement.

As we realized the importance of malnutrition and sarcopenia, and we targeted to improve the HRQoL of our patients we aimed to collect and analyze data on the BC in patients with IBD. Furthermore, we set a goal to assess the HRQoL and joint involvement as musculoskeletal manifestations may influence QoL in children with IBD.

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

In this cross-sectional study, we aimed to find the main factors determining BC parameters and assess differences in BC parameters in patients with IBD. Therefore, the BC of patients with IBD and healthy children was analyzed. Comparing anthropometric and BC parameters between patients with IBD and the entire healthy cohort, we found lower weight and BMI Z scores, and lower TBW, FFM, SMM, and BFM raw values in patients with IBD. As a next step, we showed that age, sex, and BMI were the main determinants of BC parameters (FFM, TBW, SMM, and BFM). Based on this, a propensity score matched control population was created to compare the two cohorts. FFM and TBW were still lower in the IBD group, however, there was no difference in SMM and BFM values. As a result, we concluded, that raw BC values in pediatric patients with IBD may not be informative without taking into account their association with age, sex, and BMI. Therefore, BMI based Z scores were developed based on the data of the healthy cohort that could contribute to the exact assessment of BC/SMM loss in a patient with IBD. These Z scores were applied in the same cohort of pediatric patients with IBD.

The mean Z scores of the anthropometric and BC parameters were not extremely low, none of them was lower than -1. There was no significant difference between patients with CD and UC.

As in the past decades, we recognized that malnutrition and sarcopenia are associated with extended hospitalization, increased morbidity, and mortality not just in adults but in pediatric patients as well, our focus has moved to the prevention of malnutrition. This means precise monitoring of patients with risk of malnutrition and/or sarcopenia, especially those with chronic wasting diseases, such as patients with chronic kidney disease, cystic fibrosis or even with IBD (61,62,139,140). As BMI is not sensitive enough to provide information about nutritional status, BC parameters are used. There are several recommended methods for BC measurement, but there is no gold standard method, yet. One of these is BIA, due to its cost-effectiveness, reproducibility, and easy-to-use, non-invasive technology therefore we have chosen BIA to evaluate our patients (141).

BC is influenced by genetics and also environmental factors and differs among ethnicities, races, body shapes, and sizes. Moreover, it changes with rapid growth during the adolescent period. Therefore, in pediatric patients, population-specific BC reference curves are needed to evaluate BC parameters (142). Unfortunately, in the literature the examined BC parameters, measurement techniques, and their interpretation are highly heretogenous, which further complicates the comparison of the available data. Some studies use body cell mass, LM, or FFM to characterize the biological active body mass or SMM (67,143). Other studies interpret their data by calculating indices (raw values divided by the square of the height in meters), sex-, and age-specific Z scores, or Z scores relative to height (45,94,97,98,101,103,144).

First, Forbes et al. demonstrated that FFM is related to the cube of height in 1972 (145). Then VanItallie et al. divided BMI into two parts: LM index (LM/height^2) and fat mass index (fat mass/height^2) (138). In addition, Wang et al. examined the influence of sex and population ancestry on the association of FFM and height in children and adults (146). Accepting this approach population specific FFM index and LM index reference curves were developed for children (147).

Although we found a significant association between height and BC parameters, after the ridge regression analysis age, sex and BMI remained the main determinants. This

finding is understandable with the knowledge of the operation of BIA and some previous studies (83,148–150). First of all, BMI is correlated with resistance and reactance (the raw parameters of BIA), so BIA results depend on BMI as well (83,148). Phase angle is also associated with BMI in children but not in adults (149). Furthermore, this fact was used by McCarthy et al., who evaluated muscle-to-fat ratio according to BMI, age, and sex in healthy children (150). Based on these, our findings are supported by the approach of others and the operation mechanism of BIA.

In this study TBW, FFM, and BFM showed an association with sex and BMI, and SMM correlated with sex, age, and BMI. Comparing the IBD group with the propensity score matched controls, SMM and BFM did not differ from the healthy controls. The remaining decrease in TBW and FFM support the fact that patients with IBD might suffer from a specific type of malnutrition, and suggest, that reduced SMM of the IBD group is rather a deviation from physiological than could be explained by direct wasting due to the presence of chronic illness. Therefore, due to its association with aging and age-related body size, raw values of SMM parameters seem not to be eligible for measuring the rate of muscle wasting adequately in malnourished children. Based on our results in pediatric patients with IBD, normalization according to BMI is needed to precisely screen muscle loss and to identify patients with true sarcopenia caused by chronic wasting disease. The presentation and normalization method of our data can influence the interpretation of the results as well. Our findings are supported by the study of Werkstetter et al., who presented less decreased muscle-specific values when data were corrected for height, compared to non-corrected parameters (103).

There was no difference either in anthropometric or BC parameters between patients with CD and UC. As CD can affect the whole GI tract, and systemic inflammation is more pronounced, the assumption that malnutrition and loss of LM are more frequent in CD than in UC would be obvious (151–155). On the other hand, the literature is quite controversial on this question. In our other study (see chapters 3.2., 4.2. and 5.2.), and also Boot et al. found lower FFM Z scores in patients with CD compared to UC (136). Meanwhile others did not find a difference between CD and UC patients in protein-related compartments, similar to the currently discussed study (97,105,136). Furthermore, Hill et al. reported lower body cell mass Z score in children with UC, compared to healthy controls, with the same BMI Z scores (67). In this study, the similarity could be explained

by the heterogeneity of the groups (e.g. both patients group included newly diagnosed patients and patients, whose disease did not react to conservative therapy). In contrast to our other study, where the FFM Z score was lower in CD compared to the UC group, and all included patients received anti-TNF therapy, creating more homogenous and comparable groups (136).

Nevertheless, the study had some limitations. As there is a lack of definition of pediatric sarcopenia and SMM has not been determined as a biomarker of sarcopenia, this study can only provide a rude approach to assess probable muscle loss as a potential measure of significant sarcopenia in children with IBD. Due to the fact, that this was a cross sectional study, the predictive role of the SMM Z score could not be studied. Best to our knowledge, this approach of BC Z scores counts as a novelty in the literature and everyday practice.

All in all, due to the dependence on changes in body size with aging, BC parameters have to be normalized by BMI Z score. We hope that this novel approach of SMM Z-score in monitoring muscle loss and its eligibility for precise diagnosis can help to get closer to this goal. Determination of cut-off values and definition of malnutrition and sarcopenia can be the basis of future research.

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

In this prospective observational study, BC, PA, and HRQoL were assessed and followed in 32 patients with pediatric IBD during the first six months of anti-TNF therapy. Our main findings were as follows: FFM Z score increased in the CD group, PA of patients with CD reached the level of PA in healthy controls after six months of anti-TNF therapy and we also found an elevation of SMM Z score in patients, whose SMM Z score was under -1 (risk of sarcopenia group) at the beginning of anti-TNF therapy. These patients were also younger and shorter compared to patients, whose SMM Z score was above -1 (without risk of sarcopenia).

The importance of nutritional status in pediatric IBD is an up-to-date topic, as malnutrition and/or sarcopenia is associated with a higher risk for relapse, need for surgery, reduced efficacy of biologicals affects postoperative complications, and is a predictor of adverse clinical outcomes in children with IBD (39,62,63).

In this study, we observed features of sarcopenia in patients with CD, based on normal body fat stores but decreased FFM at baseline. The observed elevation of FFM Z scores following anti-TNF therapy is in accordance with previous studies (100,143,156). BC deficits in CD may be a consequence of immune-mediated mechanisms affecting growth hormone metabolism, which releases on anti-TNF therapy (100,143).

In the UC group, we did not observe significant changes in BC parameters, however, their baseline data were also in the normal range, without severe deficits. Theoretically, systemic inflammation is a part of the pathogenesis of UC as well, which could lead to changes in nutritional status and BC (157). To the best of our knowledge, this was the first study, in which BC of pediatric patients with UC were followed during anti-TNF therapy, so we could not compare our data with other studies.

There were no statistical changes in HRQoL in our patients during the study, however, there was a tendency to increase. In contrast, previous studies showed increasing HRQoL during anti-TNF therapy (134,158). Reviewing these results in more detail, the baseline IMPACT-III score values of our patients were higher, and PCDAI values were lower at the initiation of anti-TNF therapy, compared to other studies (134,158). The higher IMPACT-III scores and lower disease activity indices in our patients at baseline reflect the upcoming practice of earlier initiation of anti-TNF therapy, especially in high-risk patients. As a result, we “maintain” the HRQoL of our patients, therefore we cannot expect “improving” HRQoL during anti-TNF treatment.

Regarding the PA, we found that the PA of patients with CD lags behind that of matched healthy controls at baseline, however, after 6 months of anti-TNF therapy, it reached the level of controls. Studies in connection with PA in patients with IBD on anti-TNF therapy are limited. Santos et al. did not describe changes in PA in adult patients with CD during 24 weeks of anti-TNF therapy (159). Other studies, evaluating PA in the pediatric IBD population reported that patients with inactive, well-controlled disease have similar PA patterns compared to healthy controls, and higher PA compared to patients with active disease (160). We assume, that the lower baseline PA may be caused by the disease activity, as in our cohort before anti-TNF therapy the disease activity was also increased. Another important factor could be the parental overprotective behavior, despite, the known benefits of PA, such as its positive effect on bone mineral density or cardiovascular condition (161). The significant increase of FFM without a significant

change in PA suggests the role of anti-TNF on mucosal healing and blockade of lipolytic and proteolytic effects of inflammatory cytokines.

The secondary aim of this study was to compare patients with or without risk of sarcopenia (SMM Z score ≤ -1 or > -1). While there is an exact definition of sarcopenia in the adult population, which includes decreased muscle mass and muscle strength, the consensus definition of pediatric sarcopenia is still missing (162). As in this study, we assessed PA without assessing muscle strength, we could estimate only the risk of sarcopenia based on SMM Z score values. We found that SMM Z score increased in patients with lower SMM Z score values at baseline, compared to patients with a baseline Z score >-1. Patients with a risk of sarcopenia were younger and shorter compared to patients whose SMM Z score was >-1. In other studies excessive weight gain in children under 10 years old and improving height Z scores in patients with early puberty were reported during anti-TNF therapy (163). These results suggest that the risk of impaired height, weight, and BC may be associated with younger age. It can be assumed based on our result and the study from Mazar et al., that the high growth velocity in this age group and the greater impact of anti-TNF agents in this population are responsible for these changes, which calls attention to the vulnerability of children in early pubertal age (164).

Weight, BMI, and height Z scores did not change throughout the study period in either CD or UC groups. According to the literature, changes in anthropometric parameters during anti-TNF therapy are controversial. More studies found increasing weight and/or BMI on IFX therapy, without significant changes in height (165–167). On the other hand, Gouldthorpe et al. and Lee et al. found statistically higher height and weight Z-scores after 34 weeks of IFX therapy (158,168). So did Borelli et al., who described improved weight and height Z scores at 6 months post induction. Later, they compared patients who completed only the induction therapy with those ones, who were treated with IFX continuously. They found, that improvement of weight and height Z scores remained only in the retreated group, however, it is important to note, that growth failure was indicative for continuing IFX therapy (169). Malik et al. also found increasing height Z scores in patients achieving clinical remission on ADA therapy. They also found a relationship between linear growth and the early stage of puberty (170). Haas et al. also discussed increasing weight and BMI Z scores in a group of patients followed for 24 months, as a consequence of faster growth velocity in early puberty. During this study

patients under 10 years old had the highest weight gain. All in all, the relationship between the treatment with anti-TNF and growth seems to have a multifactorial nature, as it may be influenced by the disease activity, clinical response, stage of puberty, and presence of baseline growth failure (171). Moreover, our findings in connection with the improving SMM Z score in younger and shorter patients with lower SMM could also be explained by these factors.

The implications of our study are limited due to the low number of patients and short follow-up period. Evaluation of changes in functional muscle parameters (grip strength), information about nutritional intake and pubertal status could complete our results.

As a conclusion, we observed improvement in FFM Z scores without the changes in BMI Z scores in children with IBD. This support the fact, that at first, BMI is not sensitive enough for assessing nutritional status, and second, anti-TNF therapy has a beneficial effect on nutritional status. Furthermore, restitution of PA in patients with CD shows optimal recovery in these patients. The lower age of patients with a risk of sarcopenia draws attention to the vulnerability of younger patients. The increasing SMM Z scores in children with a risk of sarcopenia at baseline refers also to the beneficial effects of anti-TNF therapy on nutritional status.

As malnutrition and PA affects children with IBD during a very important physical and mental developmental period, therefore encouraging them to engage in more PA, and monitoring their nutritional status should be essential goal in patient care.

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

Joint involvement is one of the most common EIMs of IBD. It is known, that arthropathies decrease HRQoL in adult patients with IBD (172). Unfortunately, only a few data are available about its role in connection with HRQoL or PA in pediatric patients, however theoretically through the pain, it could have an effect on both conditions. Moreover, caused by the inactivity may have an effect on BC as well.

In this study the prevalence of joint involvement were screened by a pediatric rheumatologist as a novelty in patients with CD, resulting in higher prevalence data than previously reported. Joint involvement including arthritis and arthralgia was associated with more severe disease, as reflected by higher PCDAI scores and lower HRQoL.

Because of the transient and fluctuating presence of oligoarthritis and its dramatic response to treatments used for exacerbations in IBD therapy, we can only estimate the incidence or prevalence of CD-related pediatric arthropathies. An additional difficulty is that arthritis and arthralgia tend to be mixed in the literature, making it impossible to estimate the real prevalence or incidence of arthritis or arthralgia. Moreover, most publications are retrospective by nature, where only clinically obvious, manifest arthritis was present, mainly detected by the gastroenterologist in charge. At the same time, detailed joint examination is not part of the routine examinations done by gastroenterologists. In our study, the prevalence was 35% and 48% for arthritis and arthralgia, respectively. Probably due to the reasons mentioned before, this is higher than in previous studies, as the rates of arthritis were reported in 3-24%, and arthralgia was reported in 14-22% of pediatric CD cases (173,174). Due to the poor prognosis caused by the presence of these EIMs of CD, it would be really important to realize its presence (175).

Another question is when symptoms of CD-associated arthropathies precede GI symptoms. These arthropathies belong to the heterogeneous enthesitis-related arthritis subgroup of juvenile idiopathic arthritis, they may manifest as sacroiliitis and/or arthritis/enthesitis, resulting in the diagnosis of juvenile idiopathic arthritis without revealing the underlying IBD. Unfortunately, pediatric data are not available, however, it is known that peripheral arthritis appears before the diagnosis of IBD in one-fifth of adult patients (176) . It is also important that 62% of patients with CD, who had arthritis at any time during the disease course, had arthritis at the onset of the disease. Therefore, it is important that every child presenting with acute or chronic arthritis should be assessed for IBD at least by a specific personal history of GI symptoms as well as a family history of IBD to obtain earlier diagnoses (22,177).

Although previous studies showed that the prevalence of enthesitis in pediatric CD is about 21%, in our cohort enthesitis was markedly uncommon (178–181). We assume that this could be explained by the younger age group compared to other studies (179).

In a large cohort of pediatric CD patients, an association of a higher baseline disease severity with the occurrence of any EIM, including arthralgia was found (174). In our cohort, joint involvement was associated with more severe disease, as reflected by

higher disease activity scores. Studies evaluating the relationship between joint involvement and disease severity later during the course of disease in childhood are rare compared to adults(174). According to Conti et al., inflammatory joint involvement is more common in patients with newly diagnosed IBD, however, there was no difference in the incidence of any joint involvement between children at the onset or early in the course of the disease, compared to patients with longer follow-up (182).

In our study, we found lower HRQoL in patients with joint involvement with an IBD-specific questionnaire. There is a lack of studies evaluating the association of arthritis and/or arthralgia and HRQoL in pediatric patients. According to studies in adults, low HRQoL is associated with disease activity, followed by the degree of arthritis, showing that musculoskeletal manifestations have a detrimental effect on HRQoL (172,183). Pediatric studies evaluated rather the effects of EIM on HRQoL, reporting a negative association (184,185).

The main aim of the therapy in musculoskeletal manifestations of IBD is to reduce inflammation and prevent disabilities and deformities (186). In our study, the rheumatological examination led to changes in systemic therapy in 25% of the patients with acute arthritis. However the use of IFX and corticosteroids are known to be effective both for IBD and musculoskeletal symptoms, using non-steroidal anti-inflamamtory drugs need caution, as it may exacerbate IBD, especially in UC (186,187).

As it is questionable, wether the therapeutic changes would have taken place even if the patients were not examined by a rheumatologist, for better symptom control and quality of life, we suggest rheumatological examination of patients with IBD by pediatric rheumatologists as well.

The main drawback of this study was the heterogeneity (in terms of disease duration, severity and treatment modalities) of the evaluated population.

All in all, real joint involvement is higher than previously described in patients with pediatric CD. As joint involvement can affect the treatment and HRQoL of patients with IBD, we recommend referring patients to a pediatric rheumatologist to achieve better symptom control and quality of care.

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6. CONCLUSIONS

Based on our studies, we can make 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 that 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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7. SUMMARY

HRQoL and prognostic factors, such as nutritional status are in the center of attention in patient care. BC analysis can not be omitted in the evaluation of nutritional status. Therefore our primary aim was to analyzise BC in patinets with IBD. We verified, that BC parameters depend on age, sex, and body size. Due to its dependence on changes in body size with aging, they have to be normalized by BMI Z score. In the lack of definition and gold standard measurement methods of sarcopenia in pediatric patients, BMI normalized SMM Z score may serve as an objective estimation of muscle loss. The determination of cut-off values may be the subject of future studies.

Using the BMI based BC Z scores, our results showed increasing FFM Z scores in children with CD during anti-TNF therapy without the changes in weight and BMI Z scores. Also, we detected elevating SMM Z scores in patients with risk of sarcopenia. These confirm the association of anti-TNF therapy and beneficial change of nutritional status. Furthermore our results highlight the known fact, that weight and BMI are not enough sensitive markers for assessment of nutritional status. The changes of PA in patients with CD could be considered as a part of optimal recovery. In addition, baseline HRQoL and disease activity indices may reflect the earlier initiation of anti-TNF therapy, which seems to be good practice for maintaining physical, social, and emotional well-being. All in all, as malnutrition and physical inactivity affect children with IBD during an important physical and mental developmental period, encouraging them to engage in more PA, and monitoring their nutritional status should be an essential goal in patient care.

We also verified that joint involvement is higher in children with CD, than previously recognized by gastroenterologists. As it affects 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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APPENDIX

Appendix 1. A

Dátum:_____

Fizikai aktivitást mérő kérdőív

Név:_____ Kor:_____ Nem: Fiú / Lány

Kedves kitöltő!

Ennek a kérdőívnek a segítségével szeretnénk megbecsülni fizikai aktivitásodat az utóbbi 7 napban (elmúlt egy hétben). Ebbe beletartozik a sport vagy a tánc, aminek hatására leizzadsz, vagy elfáradnak a lábaid, vagy játékok, amelyek gyorsabb légzést okoznak számodra, mint a fogócska, az ugróiskola, futás, mászás és egyebek.

Emlékezz:

1. Nincsenek jó és rossz válaszok – ez nem egy teszt
2. Kérlek olyan őszintén és pontosan válaszolj, ahogy csak tudsz – ez nagyon fontos.

---

1. Fizikai aktivitás a szabadidődben: Részt vettél /csináltál bármit a lentebb levő mozgásformák közül az utóbbi 7 napban (egy hétben)? Ha igen, hányszor? (Soronként csak egy kört jelölj be)

	Egyszer sem	1-2	3-4	5-6	7-szer vagy többször
Atlétika	o	o	o	o	o
Karate	o	o	o	o	o
Judo	o	o	o	o	o
Vívás	o	o	o	o	o
Kick-box	o	o	o	o	o
Boksz	o	o	o	o	o
Ritmikus sportgimnasztika	o	o	o	o	o
Lovaglás	o	o	o	o	o
Ugrókötelezés	o	o	o	o	o
Evezés/kenuzás	o	o	o	o	o
Úszás	o	o	o	o	o
Vízilabda	o	o	o	o	o
Tánc	o	o	o	o	o
Biciklizés	o	o	o	o	o
Kocogás vagy futás	o	o	o	o	o
Aerobik	o	o	o	o	o
Kosárlabda	o	o	o	o	o

1

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Gördeszkázás.....	o	o	o	o	o
Baseball, puhalabdajátékok.....	o	o	o	o	o
Sétálás edzésként.....	o	o	o	o	o
Amerikai foci.....	o	o	o	o	o
Tollaslabda.....	o	o	o	o	o
Fogócska.....	o	o	o	o	o
Foci.....	o	o	o	o	o
Street hockey.....	o	o	o	o	o
Röplabda.....	o	o	o	o	o
Floor ball.....	o	o	o	o	o
Gyorskorcsolya.....	o	o	o	o	o
Jégkorcsolya.....	o	o	o	o	o
Sífutás.....	o	o	o	o	o
Jégkorong/ringette.....	o	o	o	o	o
Egyéb:	o	o	o	o	o
.....	o	o	o	o	o
.....	o	o	o	o	o

2. Az utóbbi 7 napban a testnevelésórán milyen gyakran voltál nagyon aktív (keményen játszottál, futottál, ugráltál, dobtál)? (Csak egy válaszlehetőséget jelölj meg)

Nem veszek részt a testnevelésórákon..... o
Szinte soha..... o
Néha..... o
Elég gyakran..... o
Mindig..... o

3. Az utóbbi 7 napban mit csináltál a legtöbbször az *iskolai szünetekben*? (Csak egy válaszlehetőséget jelölj meg)

Ültem (beszélgettem, házifeladatot írtam)..... o
Álldogáltam és sétálgattam..... o
Futkároztam és játszottam (sportoltam) egy kicsit o
Futkároztam és sokat játszottam (sportoltam)..... o
Általában mindig futkározok és kimerítően játszok o

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4. Az utóbbi 7 napban mit csináltál *ebédszünetben* (az ebédelésen kívül)? (Csak egy válaszlehetőséget jelölj meg)

Ültem (beszélgettem, házi feladatot írtam)..... o
Álldogáltam és sétálgattam..... o
Futkároztam és játszottam (sportoltam) egy kicsit..... o
Futkároztam és sokat játszottam..... o
Általában mindig futkározok és kimerítően játszok ..... o

5. Az utóbbi 7 napban hány *hétköznap délután/este* sportoltál, táncoltál vagy játszottál valamilyen játékot, amiben nagyon aktívan részt kellett venned? (Csak egy válaszlehetőséget jelölj meg)

Egyszer sem..... o
1-szer a múlt héten..... o
2-3-szor a múlt héten..... o
4-szer a múlt héten..... o
5-ször a múlt héten..... o

6. Az utóbbi 7 napban, hány *délutánt/estét* töltöttél sporttal, tánccal vagy olyan játékkal, amelyben nagyon aktív voltál? (Csak egy válaszlehetőséget jelölj meg)

Egyszer sem..... o
1-szer a múlt héten..... o
2-3-szor a múlt héten..... o
4-szer a múlt héten..... o
5-ször a múlt héten..... o

7. A *legutóbbi hétvégén*, hányszor sportoltál, táncoltál vagy vettél részt nagyon aktívan valamilyen játékban? (Csak egy válaszlehetőséget jelölj meg)

Egyszer sem..... o
1-szer..... o
2-3-szor..... o
4-szer ..... o
5-ször ..... o

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8. Az alábbiak közül *melyik volt jellemző* Rád leginkább az utóbbi 7 napban? Mielőtt eldöntenéd a választ, olvasd el mind az 5 válaszlehetőséget.

A. Majdnem, vagy az összes szabadidőmet olyan tevékenységekkel töltöttem, amelyek kevés fizikai erőkifejtést (pl. sportolás, táncolás, játszás, vagy bármi más fizikailag aktív dolog) igényelnek..... o
B. Néha (1-2-szer a múlt héten) fizikailag aktívan töltöm a szabadidőmet (pl.: részt veszek sportjátékokban, elmegyek futni, úszni, biciklizni, aerobikozni)..... o
C. Gyakran (3-4-szer a múlt héten) voltam aktív fizikailag a szabadidőmben (pl.: részt veszek sportjátékokban, elmegyek futni, úszni, biciklizni, aerobikozni) ..... o
D. Elég gyakran (5-6-szor a múlt héten) voltam aktív fizikailag a szabadidőmben(pl.: részt veszek sportjátékokban, elmegyek futni, úszni, biciklizni, aerobikozni)..... o
E. Nagyon gyakran (7 vagy több alkalommal) voltam aktív fizikailag a szabadidőmben (pl.: részt veszek sportjátékokban, elmegyek futni, úszni, biciklizni, aerobikozni)..... o

9. Jelöld be, hogy milyen gyakran voltál aktív fizikailag az adott napokon (pl. sportolás, táncolás, játszás, vagy bármi más fizikailag aktív dolog) a múlt héten.

	Egyáltalán nem	Ritkán	Közepesen	Gyakran	Nagyon gyakran
Hétfő.....	o	o	o	o	o
Kedd.....	o	o	o	o	o
Szerda.....	o	o	o	o	o
Csütörtök.....	o	o	o	o	o
Péntek.....	o	o	o	o	o
Szombat	o	o	o	o	o
Vasárnap.....	o	o	o	o	o

10. Voltál beteg a múlt héten, vagy történt valami ami hátráltatott az átlagos normális fizikai aktivitásodban? (Csak egyet jelölj meg)

Igen ..... o

Nem ..... o

Ha igen, mi hátráltatott? _____

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Appendix 2.

IMPACT-III

Magyarul/Magyarország – Hungarian/Hungary

ÉLETMINŐSÉGRE VONATKOZÓ KÉRDŐÍV OLYAN GYERMEKEK RÉSZÉRE, AKIK GYULLADÁSOS BÉLBETEGSÉGBEN SZENVEDNEK

ÚTMUTATÓ

Az alábbiakban 35 kérdésből álló kérdőívet találsz, amely **gyulladásos bélbetegségben (Crohn betegség, colitis ulcerosa)** szenvedő gyermekekre vonatkozik. A kérdések a gyulladásos bélbetegséggel történő együttélésedre vonatkoznak.
A kérdések egyik része például a fájdalomaiddal kapcsolatosak, mások az általános közérzetedre, problémáidra vonatkoznak.

Minden kérdés után egy-egy négyzetet találsz az öt lehetséges válasz felett.
Kérjük, **kereszttel jelöld meg azt a négyzetet, amely számodra a legmegfelelőbb válasz felett van.**

Először is egy példa:
Kérdés: Mennyire félsz a tigrisektől?

☐	☐	☐	☒	☐
Egyáltalán nem félek	Egy kicsit félek	Közepesen félek	Félek	Nagyon félek

Tehát ez a személy **fél** a tigrisektől.

☐	☒	☐	☐	☐
Egyáltalán nem félek	Egy kicsit félek	Közepesen félek	Félek	Nagyon félek

Ez a személy **kicsit fél** a tigrisektől.

Kérjük, **minden kérdésre** válaszolj.
Ha nem érted a kérdést, akkor kérj segítséget.
Sok sikert a kérdéssor kitöltésében... továbbá előre is köszönjük a fáradozásod!

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1. Kérdés	**Az elmúlt két hétben mennyire fájt a hasad?**

☐ Egyáltalán nem	☐ Alig fájt	☐ Kicsit fájt	☐ Meglehetősen fájt	☐ Nagyon fájt

2. Kérdés	**A gyógyszerek, tabletták szedése zavar.**

☐ Egyáltalán nem	☐ Alig zavar	☐ Kicsit zavar	☐ Meglehetősen zavar	☐ Nagyon zavar

3. Kérdés	**Az elmúlt két hétben hányszor akadályozott meg a gyulladásos bélbetegséged abban, hogy azt egyél, amit szeretnél?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

4. Kérdés	**Az elmúlt 2 hétben milyen gyakran aggódtál amiatt, hogy a betegséged fellángol, vagyis tüneteid újra megjelennek?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

5. Kérdés	**Milyen mértékben aggódsz amiatt, hogy olyan betegséged van, amely nem múlik el csak úgy?**

☐ Egyáltalán nem	☐ Alig zavar	☐ Kicsit zavar	☐ Meglehetősen zavar	☐ Nagyon zavar

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6. Kérdés	**Az elmúlt 2 hétben milyen volt az erőnléti állapotod?**

☐	☐	☐	☐	☐
Nagyon sok energiám volt	Elég sok energiám volt	Közepes energiám volt	Kis energiám volt	Semmi energiám nem volt

7. Kérdés	**Mit gondolsz a súlyodról?**

☐	☐	☐	☐	☐
Nagyon elégedett vagyok a súlyommal	Elégedett vagyok a súlyommal	Közepesen vagyok elégedett a súlyommal	Elégedetlen vagyok a súlyommal	Nagyon elégedetlen vagyok a súlyommal

8. Kérdés	**Milyen mértékben érinti gyulladásos bélbetegséged a családodat?**

☐	☐	☐	☐	☐
Egyáltalán nem érinti	Kicsit érinti	Közömbös hatással volt a családomra	Rossz hatással	Szörnyű hatással

9. Kérdés	**Az elmúlt 2 hétben milyen gyakran kellett gyulladásos bélbetegséged miatt bizonyos dolgokról lemondanod (hobby, sport, szórakozás)?**

☐	☐	☐	☐	☐
Soha	Ritkán	Olykor	Gyakran	Nagyon gyakran

10. Kérdés	**Az elmúlt 2 hétben milyen gyakran zavart a hasmenésed (híg vagy gyakori székelés)?**

☐	☐	☐	☐	☐
Soha	Ritkán	Olykor	Gyakran	Nagyon gyakran

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11. Kérdés	**Milyen gyakran aggódsz a jövőbeli egészségi állapotod miatt?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

12. Kérdés	**Milyen gyakran gondolod igazságtalannak azt, hogy gyulladásos bélbetegséged van?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

13.Kérdés	**Az elmúlt 2 hétben volt-e olyan, hogy dühös voltál, hogy gyulladásos bélbetegséged van?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

14. Kérdés	**Mennyiben gondolod, hogy a gyulladásos bélbetegséged miatt túl sok szabály és korlátozás ér?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

15. Kérdés	**Milyen mértékben vagy elégedett a külsőddel?**

☐ Úgy gondolom, nagyszerűen nézek ki	☐ Úgy gondolom, jól nézek ki	☐ Úgy gondolom, közepesen nézek ki	☐ Úgy gondolom, rosszul nézek ki	☐ Úgy gondolom, szörnyen nézek ki

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16. Kérdés	**Érzel-e szégyenérzetet a beleid állapota miatt?**

☐	☐	☐	☐	☐
Egyáltalán nem	Alig	Közepesen	Meglehetősen	Nagyon

17. Kérdés	**Voltak vidám pillanataid az elmúlt két hétben?**

☐	☐	☐	☐	☐
Nagyon gyakran	Gyakran	Olykor	Ritkán	Soha

18. Kérdés	**Nehezebb barátságokat kötnöd, mert gyulladásos bélbetegséged van?**

☐	☐	☐	☐	☐
Egyáltalán nem nehezebb	Kicsit nehezebb	Közepesen nehéz	Meglehetősen nehezebb	Sokkal nehezebb

19. Kérdés	**Milyen gyakran aggódsz amiatt, hogy a székleted vért tartalmaz?**

☐	☐	☐	☐	☐
Soha	Ritkán	Olykor	Gyakran	Nagyon gyakran

20. Kérdés	**Aggódsz-e amiatt, hogy a gyulladásos bélbetegséged miatt nem tudsz elmenni egy randevúra, vagy nem lesz barátod/barátnőd?**

☐	☐	☐	☐	☐
Egyáltalán nem aggódom	Kicsit aggódom	Közepesen aggódom	Meglehetősen aggódom	Nagyon aggódom

21. Kérdés	**Az elmúlt 2 hétben milyen gyakran fájt nagyon a hasad?**

☐	☐	☐	☐	☐
Soha	Ritkán	Olykor	Gyakran	Nagyon gyakran

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22. Kérdés	**Mennyire viselnek meg azok a vizsgálatok, amin át kell menned?**

☐ Egyáltalán nem	☐ Nagyon kicsit	☐ Kicsit megviselnek	☐ Nagyon megviselnek	☐ Utálom ezeket

23. Kérdés	**Erőszakoskodik-e veled más gyerek, vagy hagy ki dolgokból a gyulladásos bélbetegséged vagy annak kezelése miatt?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

24. Kérdés	**Milyen gyakran félsz attól, hogy megoperálnak?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

25. Kérdés	**Az elmúlt 2 hétben milyen gyakran aggódtál amiatt, hogy bekakilsz vagy nem érsz időben a WC-re?**

☐ Soha	☐ Ritkán	☐ Olykor	☐ Gyakran	☐ Nagyon gyakran

26. Kérdés	**Próbálod-e titokban tartani gyulladásos bélbetegségedet a többi ember előtt?**

☐ Nem, egyáltalán nem próbálom	☐ Nem igazán próbálom	☐ Egy kicsit próbálom	☐ Eléggé próbálom	☐ Igen, nagyon próbálom

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27. Kérdés	**Megnehezíti-e a gyulladásos bélbetegséged, hogy utazzál, vagy hogy nyaralni menjél?**

☐	☐	☐	☐	☐
Nem, egyáltalán nem	Kicsit	Meglehetősen	Nagyon	Igen, iszonyúan

28. Kérdés	**Hogy érezted magad az elmúlt 2 hétben?**

☐	☐	☐	☐	☐
Nagyszerűen	Jól	Közepesen	Rosszul	Szörnyen

29. Kérdés	**Boldog vagy az életeddel?**

☐	☐	☐	☐	☐
Igen, nagyon boldog	Boldog	Se nem boldog, se nem boldogtalan	Boldogtalan	Nagyon boldogtalan

30. Kérdés	**Van olyan személy, akivel tudsz beszélni a gyulladásos bélbetegségedről?**

☐	☐	☐	☐	☐
Mindig	Gyakran	Néha	Ritkán	Soha

31. Kérdés	**Az elmúlt 2 hétben milyen gyakran kellett „szellentened"?**

☐	☐	☐	☐	☐
Soha	Ritkán	Olykor	Gyakran	Nagyon gyakran

32. Kérdés	**Az elmúlt 2 hétben mennyire voltál fáradt?**

☐	☐	☐	☐	☐
Egyáltalán nem	Kicsit	Közepesen	Meglehetősen	Nagyon

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33. Kérdés	**Mit gondolsz a magasságodról?**

☐	☐	☐	☐	☐
Nagyon elégedett vagyok vele	Elégedett vagyok a magasságommal	Közepesen elégedett vagyok	Nem vagyok elégedett	Szörnyen elégedetlen vagyok

34. Kérdés	**A gyulladásos bélbetegséged mennyire engedi, hogy olyan sportot űzz, amit szeretnél?**

☐	☐	☐	☐	☐
Nagyon gyakran	Gyakran	Olykor	Ritkán	Soha

35. Kérdés	**Az elmúlt 2 hétben milyen gyakran tudtál járni iskolába? (Ha éppen iskolai szünet vagy nyári szünet van, úgy válaszolj, mintha lenne iskola)**

☐	☐	☐	☐	☐
Mindig	Legtöbb nap	Minden másnap	Néhány naponta	Soha