SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Relationship between nutritional status and childhood neoplastic and inflammatory bowel diseases

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I. INTRODUCTION

Assessing and evaluating nutritional status is an integral part of patient care, since abnormal nutritional status can significantly influence the outcome of the disease and represents a medical condition requiring treatment. The primary goal of the assessment is to recognize the lack or excessive intake of nutrients and calories as early as possible. There is no single method which can completely evaluate the nutritional status of patients; therefore, combined use of multiple methods is recommended.

Assessment of nutritional status is an essential part of physical examination. If performed repeatedly, it enables us to recognize pathological changes due to acute and chronic wasting conditions. In addition to undernutrition, screening should involve overnutrition as well because of high and increasing prevalence of childhood obesity.

The concept of malnutrition (poor nutrition) means the deficiency, excess or imbalance of an individual's energy and/or nutrient intake, which has a measurable adverse effect on the composition and function of the organism, and clinical outcome of diseases. Malnutrition can present as undernutrition, which includes wasting, starvation, and low weight, as well as the absence or insufficiency of micronutrients. A child with a low body weight may be wasting, starving, or both conditions may be present at the same time. Another possibility of the malnutrition spectrum is overweight and obesity. It seems paradoxical, but it can be established that some elements of under- and overnutrition may overlap with a harmful outcome. Some aspects of undernutrition may be present in overweight or obese children. The overlap between undernutrition and obesity may become pronounced when associated with certain diseases and their treatment. One of the most important consequences of malnutrition is an unfavorable outcome of diseases, which may result in a worse than expected treatment response, even in the death of patient, not to speak about poor quality of life.

II. BACKGROUND

II.1. Childhood malnutrition in Hungary

Nowadays in Hungary, undernutrition occurs at a very low rate both in toddlers and in elementary school age. The rate gradually decreases from 8% to 1.5% between the age groups of 5- and 19-year-old children and young adults. On the other hand, the prevalence of obesity, based on body mass index (BMI), gradually increases from early childhood to the age of 18, reaching 12.6%.

II.2. Childhood neoplastic diseases

About 400,000 new neoplastic diseases ("cancer") develops in patients between the ages of 0 and 19 years annually, worldwide. Cancer is the leading cause of death in children and adolescents after accidents. In high-income countries, more than 80% of children with cancer will be cured, while in low-income countries this rate does not reach 30%. In addition to geographic location, survival is influenced by the type of tumor (over 80% in acute lymphoblastic leukemia (ALL)), its stage, the drugs and their side effects used for treatment, and complications associated with treatment, such as infections. According to our current knowledge, the development of childhood cancers cannot be prevented, and screening tests are not suitable for their effective, early detection. At the same time, the likelihood of survival can be increased with early diagnosis, the application of appropriate therapeutic protocols and the full use of supportive treatment, which also includes nutritional therapy.

In Hungary, about 700-800 children receive anti-tumor treatment every year. According to data from the National Children's Tumor Registry, between 2015 and 2019, 1115 children aged 0-14 were diagnosed with a malignant hematological diseases and solid tumors.

II.3. Importance of good nutritional status in childhood neoplastic diseases

Malnutrition, i.e., both undernutrition and overnutrition of children with malignancies were correlated with higher relapse and mortality rates and a higher risk for developing infection. The nutritional status of a child with a cancer has an impact on treatment (e.g. dosage of medication), treatment-related side effects and recovery. The nutritional status of most children is also affected by the disease itself. Unfortunately, even today, many undernourished children with cancer are not recognized in time, and therefore, they do not get adequate nutritional therapy.

Depending on the type of cancer, weight loss occurs in 30-80% of patients during treatment, more pronounced in solid tumors than in hematological malignancies. Weight loss is an important prognostic factor of the disease: the greater the weight loss, the shorter the survival time. Significant weight loss of more than 20% of body weight cannot be reversed with nutritional supplements.

Parallel to the rising prevalence of obesity worldwide, the problem has also appeared among patients with childhood neoplastic diseases, mainly with leukemia, both at the time of diagnosis, during and after treatment. Overweighted children have lower overall and event-free survival rates at the time of diagnosis compared to their peers with adequate nutrition. Increased mortality is primarily associated with an increased risk of relapse and changes in drug metabolism.

During the growth and development of the child, the physiological processes are constantly changing, including the pharmacokinetics and pharmacodynamics of drugs. As a result, the toxicity profile and unpredictable effectiveness of the drugs can potentially have particularly harmful consequences, especially during the treatment of undernourished or overweighted, obese cancer patients. Deep insight into the ideal body weight and body composition needed to calculate precise drug doses can be the basis for planning individual chemotherapy treatment in the future.

II.4. Cancer cachexia

Cachexia is the irreversible atrophy of terminally ill patients. It is associated with chronic inflammatory conditions and cancer. Cancer cachexia is characterized by significant weight loss, loss of appetite, weakness, and anemia, as well as systemic inflammation, negative protein and energy balance, and involuntary loss of fat-free body mass with or without adipose tissue loss. Clinically, cancer cachexia in children manifests in inability to thrive and grow. Cachexia is accompanied by changes in body composition and disturbances in the balance of the biological system. Loss of skeletal muscle mass is the most obvious sign of cancer cachexia and is accompanied by the depletion of fat and heart muscle. Due to the inappropriate myelination of the child's brain, development of cognitive function may suffer impairment. Therefore, it is essential to recognize and prevent cachexia associated with the tumor or its treatment as early as possible. Undernutrition should be vigorously prevented and treated with nutritional therapy and application of appetite enhancers to avoid possible irreversible damages to somatic and mental development.

II.5. Inflammatory bowel diseases

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which clinically includes Crohn's disease (CD), ulcerative colitis (UC) and "IBD-unclassified". In IBD, intestinal inflammation is clinically characterized by abdominal pain, diarrhea, bloody stools, weight loss. The pathomechanism is characterized by the infiltration of the intestinal wall by neutrophils and macrophages which produce cytokines, proteolytic enzymes, and free radicals. IBD is a life-long, incurable disease that can develop even in young children and may affects both men and women. Its incidence and prevalence increased significantly in the second half of the 20th century. The highest prevalence of IBD has been observed in Northern Europe and North America. Since 1990 it has been stable or started to decrease in Western countries, but the incidence rate has increased in newly industrialized countries of Asia, Africa, and South America. The incidence of childhood IBD in Hungary is 7.8/100,000 people, the incidence of CD is twice that of UC (4.8/100,000 vs. 2.3/100,000).

The mortality rate of IBD is not higher than that of the general populations. Due to its chronic course, however, it requires lifelong treatment, and due to hospitalizations and increasing rates of surgery, it represents an increasing financial burden for health care systems. Even with a well-controlled disease, the quality of life of patients is worse than their healthy peers.

The course of both CD and UC is characterized by alternating symptom-free periods (remission) and flare-ups (relapse). The activity of the disease can be characterized by activity indices. The Pediatric Crohn’s Disease Activity Index (PCDAI) is used to characterize CD, while the Pediatric Ulcerative Colitis Activity Index (PUCAI) is used to characterize CU. Higher scores indicate increased disease activity.

II.6. Changes in nutritional status in pediatric inflammatory bowel diseases

Some 25% of IBD is recognized in childhood adolescent (what does that mean?) patients. A special childhood characteristic of the disease is the development of growth failure as a complication of chronic intestinal inflammation. Achieving adequate growth is also an indicator of successful therapy. Undernutrition and growth retardation are also one of the most characteristic extraintestinal manifestations in childhood, especially in CD. The proportion of undernourished children varies between 10-32% in CD and 7-10% in UC worldwide.

However, in the last few years, overweight and obesity have emerged among the most serious public health problems in children and adolescents. In addition to the United States of America and Western European countries, the problem also became noticeable in Central Europe. According to the latest results, there is a shift in the nutritional status of adults with IBD, and more overweight and obese patients can be observed among them. This can delay the establishment of the diagnosis of IBD, moreover, overweight adults with IBD have higher morbidity, greater disease activity, surgical intervention may become necessary earlier, and perianal complications are more frequent than among properly or undernourished counterparts. Obese adults are more likely to have IBD flares than patients with normal weight.

Among children with newly diagnosed IBD, obesity is presented in 1.9–10% of CD and 8.4–34% of UC, depending on geographic location. An Israeli study found that children with IBD in the lower and higher ranges of the BMI percentile spectrum had higher disease activity, more frequent disease exacerbations, and more frequent need for biologic therapy.

II.7. The relationship between systemic inflammation and nutritional status

In developed countries undernutrition is primarily associated with comorbid conditions. The causes of undernutrition due to diseases include loss of nutrients, increased energy consumption, reduced nutrient intake and altered nutrient utilization, and many other external factors (e.g., poverty, unbalanced diet).

The redox imbalance induced by oxidative stress and the persistent production of proinflammatory mediators represent the pathophysiological basis of sarcopenia observed in inflammatory diseases, including cancers and inflammatory bowel diseases. Sarcopenia is a degenerative loss of skeletal muscle mass, quality and strength, a common phenomenon of the natural aging process. It occurs secondary to chronic diseases in childhood. Sarcopenic obesity is characterized by the loss of muscle and the simultaneous pathological accumulation of adipose tissue contributed by physical inactivity and high energy intake, chronic comorbidity, and systemic inflammation. Cancer cachexia is associated with a hypercatabolic state, while children with inflammatory bowel disease are primarily characterized by sarcopenia associated with anabolic resistance. Systemic inflammation, increased cytokine outflow and its adverse effect on nutritional status are present in both diseases.

Obesity is associated with an increased risk of several immune mediated conditions, such as rheumatoid arthritis and psoriasis, which have a similar genetic and immunological background as IBD. Adipose tissue is characterized by the production of pro- and anti-inflammatory cytokines, collectively known as adipokines. Adiponectin is produced exclusively by adipocytes, it has a complex interaction with several inflammatory pathways, and shows a certain degree of structural homology with tumor necrosis factor-alpha (TNF-α), a cytokine that plays a significant role in the pathogenesis of IBD. The effect of adiponectin is anti-inflammatory. Leptin and resistin increase the synthesis of pro-inflammatory cytokines such as interleukin-1, interleukin-6, and TNF-α, and synergistically, pro-inflammatory cytokines promote leptin expression in inflamed tissues. Mesenteric adipose tissue is a source of anti-inflammatory adipokines and several pro-inflammatory cytokines. The levels of circulating proinflammatory cytokines increase in parallel with increasing visceral adipose tissue mass. The expression of the TNF-α gene can be detected in the mesenterial "creeping fat" characteristic of Crohn's disease, which creeps within the intestinal wall, and synthesizes interleukin-17 and CRP.

Following an unbalanced, excessively refined carbohydrate-, and high-fat-containing Western-style diet is also characteristic of the development of IBD and obesity. At the same time, the appearance of both diseases is characterized geographically by spreading from the West to East.

It is a well-known fact that the breakdown of the diversity of intestinal flora has a pathogenetic role in both obesity and IBD. The composition of the intestinal flora is determined by many factors, including the individual's diet. A Western-style diet worsens diversification, while high consumption of vegetables and fruits improves it. Disruption of the composition of the intestinal flora leads to increased intestinal permeability, which results in constant, mild inflammation, in an increase in the visceral adipose tissue and mesenterial “creeping” fat associated with reduced adiponectin release. Excessive caloric intake contributes to the continuous presence of mild inflammation by inducing oxidative stress through metabolic changes. The combined effect of the above-mentioned factors can result in the release of proinflammatory cytokines and the development of various diseases, including IBD, in susceptible individuals.

II.8. Assessment of nutritional status in childhood

The assessment of nutritional status is based on anthropometric measurements, biochemical tests, physical examination, and evaluation of a food diary (determination of consumed nutrients and calories) and more recently, body composition analysis. By itself, neither of them provides a comprehensive picture of the nutritional state of the patient. However, it is often not possible to use all of them at the same time.

Anthropometric methods include the measurement of body weight, height, triceps skinfold and upper arm thickness, the expected body weight-for-height (WFH), which is a sensitive parameter to detect protein and energy malnutrition, and the calculation of the body mass index (BMI). To follow the short- and long-term changes in nutritional status, it is necessary to carry out regular measurements, then it is recommended to plot the results on growth curves. The ideal body weight (IBW) percentage is used as an indicator of nutritional status. It can be used to judge primarily undernutrition, but also the degree of overnutrition, too. There are several methods for determining the ideal body weight, which show surprisingly different results in the case of the same patient, and there is no consensus on which is the best method, so expressing it in % can also give different results.

The Nutrition Working Group of the International Society of Pediatric Oncology (SIOP) recommends standard methods for assessing the nutritional status of children with cancer, considering its ease of implementation and cost-effectiveness. These include anthropometric methods: body weight, height, upper arm circumference, triceps skinfold thickness determination and derived parameters such as standard deviation (Z-score) of expected body weight for age (WFA), body mass index (BMI), expected body weight-for-height (WFH) analysis. Assessment of the nutritional status of a child with inflammatory bowel disease includes the same factors as for children with cancer, however, only BMI calculation has been recommended in this patient group.

In addition to the indicators above, a less frequently used derived anthropometric parameter is the ideal body weight percentage (IBW%). Determining the ideal body weight for oncology patients is also essential for calculating the appropriate drug dose. The combined use and evaluation of IBW% and BMI percentile values is not common when assessing and monitoring the nutritional status of healthy or sick children. One of the reasons for abandoning the calculation of IBW% may be that it requires multiple steps, it is time-consuming and difficult to calculate accurately by hand, and no organizations or national statistical database track IBW% over time, making longitudinal monitoring difficult. Generally only BMI Z-score value calculation is advised for assessment nutritional status by WHO, the international pediatric oncology and pediatric gastroenterology societies, where a child below -2 Z-score is considered undernourished and obese above 2 Z-score.

The adverse effect of weight loss on morbidity and mortality has been known since the 1930s. Weight loss greater than 10% is associated with an increased risk of morbidity and mortality regardless of the underlying disease process or the treatment used. Nevertheless, assessing the degree of weight loss is not part of the daily routine and is not included in the recommendations of any international children's oncology or gastroenterology societies in the assessment and monitoring of the patient's nutritional status.

In addition to anthropometric measurements, laboratory tests are useful, but they are not an essential part of assessing nutritional status. Signs of malnutrition can be detected with physical examination, so signs of insufficient energy and/or nutrient deficiency can be detected. Knowledge of diet-related information is an essential component of the nutritional survey, providing information on the quantity and quality of the food consumed.

In addition to simple anthropometric methods, more attention is paid to techniques suitable for determining body composition. Some of them are not available in the clinical practice and are used for research purposes. Criterion methods include the double photon absorption technique (DEXA), computed tomography (CT) and magnetic resonance imaging (MRI), which can determine the amount and ratio of fat mass, fat-free mass, and muscle mass. Although these methods are available in practice, their regular use is not practical, they require a special computer program and an experienced user. The rapid bioelectrical impedance analysis (BIA), which is suitable for longitudinal examination of the patient's condition, unfortunately provides inaccurate results compared to the previous criterion techniques. Disadvantage of it is that in many cases race-, nation- and disease-specific reference data are not available.

III. OBJECTIVES

The primary goal of the scientific work was to assess the nutritional status of children suffering from chronic diseases and using methods which are available daily in the Hungarian healthcare data system, and which are not burdensome for a seriously ill patient, even for a patient in a very poor general condition, and which are easily reproducible. Thus, the primary tool of our research was the measurement of body weight and body height and the calculation of anthropometric indicators from these data.

III.1. Assessing the nutritional status of children with leukemia and solid tumors; analysis of the relationship between nutritional status and disease course

1. The aim was - using a retrospective, longitudinal method - to determine the prevalence and severity of undernutrition among children suffering from malignant diseases in Northeast Hungary during the course of active anticancer treatment, since no similar survey has been carried out in our country so far.
2. To use anthropometric parameters in addition to BMI determination, such as ideal body weight % presented as the ratio of the actual body weight to the expected body weight for height and weight loss %, to find a simple, easy-to-calculate indicator that more reliably detects the development of undernutrition even in children with normal nutritional status (e.g., normal BMI).
3. To examine the correlation between the nutritional status of patients and survival.

II.2. Assessment of the nutritional status of children with Crohn's disease and ulcerative colitis; analysis of the relationship between nutritional status and disease course

1. The aim was to assess the prevalence of malnutrition in a cross-sectional study focusing on obesity at the time of diagnosis among children with IBD in Hungary.
2. To use other anthropometric parameters such as BW and WFH Z-score and IBW % addition to BMI, to assess nutritional status.
3. To compare patients with Crohn's disease and ulcerative colitis based on their nutritional status.
4. To look for a correlation between the nutritional status of patients and the activity of the disease at the time of diagnosis.

IV. MATERIALS and METHODS

IV.1. Patients with neoplastic disease

Children between the ages of 1 and 18 years, diagnosed and treated between 1999 and 2009 at the Pediatric Hematology-Oncology Tertiary Care Center of the Pediatric Clinic of the University of Debrecen participated in the retrospective follow-up study. During this period, 218 children received active anticancer treatment according to the current guidelines of the Hungarian Pediatric Oncology-Hematology Group. The patients were followed up for five years. Forty-four patients did not participate in the study, those who did not attend care after treatment (lost-to-follow up) or those who continued their treatment at another pediatric oncology center. Finally, 174 patients were included in the study. The study was approved by the Scientific Research Ethics Committee of the Hungarian Medical Council (DE KK RKEB/IKEB No. 5623-2020), and the legal representatives of the participating patients gave their written consent.

IV.2. Patients with inflammatory bowel disease

CD or UC children between 0 and 18 years old, diagnosed between 2010-2016 and registered in the Hungarian Pediatric IBD Register (HUPIR) participated in the cross-sectional study. The number of patients was 699 in CD and 328 in UC. Those who did not have sufficient data on ileocolonoscopy, histological samples taken from the same region, and those who did not undergo a detailed diagnostic examination (endoscopy, histology, radiology) and those patients who did not agree to the study were excluded. The database of the register includes the patient's age, sex, height, body weight, and disease activity index. The study was approved by the Scientific Research Ethics Committee of the Hungarian Medical Research Council (10434/2012/EKU (175/PI/12).

IV.3. Assessment of nutritional status

Patients' body weight (expressed in kg) and body length or height (expressed in cm) were collected from the medical documentation and the registry database. The standard deviation values (SDS; Z-score) of BW, WFH and BMI (kg/m2) were calculated based on the reference values of the Hungarian longitudinal child growth survey. IBW% was defined as the 50th percentile of the currently measured BW*100/WFH.

In children with cancer, the data were recorded at the time of diagnosis, during treatment when the greatest weight loss was measured and at the end of treatment. In children with inflammatory bowel disease, we performed calculations using body weight and height values measured at the time of diagnosis.

Based on the WHO criteria, the patient is considered undernourished if the BW, WFH or BMI Z-score < -2.0, obese if the Z-score > 2. If the IBW% is below 90%, the patient is considered undernourished, obese if IBW% >120%. The degree of undernutrition can be determined based on the IBW%: the patient is severely undernourished if the IBW% is <70%, moderately undernourished if 70-80% and mildly undernourished if it is between 80-90%.

For children with cancer, we also determined the weight loss % (WL%). Body weight measured at the time of diagnosis was taken as the starting point. Based on this, the child is severely undernourished if the amount of weight loss exceeds 30% of the body weight, moderately undernourished between 20-30% and mildly if the weight loss is between 10-20%.

The Hungarian reference curves do not contain data above the height of 184 cm for boys and 175 cm for girls, so it was not possible to determine WFH and IBW% in 44 extensively tall adolescents with IBD. Therefore, analyzes influenced by body height were performed only in patients lower than the above limits (N=983) of. However, this loss of data did not affect the statistical analysis, as the large number of patients allowed the calculation to be performed.

IV.4. Endpoints in patients with neoplastic disease

In the case of children with hematologic neoplasia and malignant solid tumors, we investigated the effect of nutritional status on overall survival (OS) and event free survival (EFS). The endpoint in both cases was 5-year survival.

IV.5. Assessment of disease activity in inflammatory bowel disease

Disease activity was determined using validated clinical activity indices: the Pediatric Ulcerative Colitis Activity Index (PUCAI) and the Pediatric Crohn's Disease Activity Index (PCDAI). PUCAI classifies the disease as inactive below 10 points, mild between 10 and 34 points, moderately severe between 35 and 65 points, and severe above 65 points. The PCDAI categories are as follows: inactive disease <10 points, mild between 11-29 points, moderate between 30-37 points and severe above 37.5 points.

IV.6. Applied statistical methods in the retrospective, longitudinal study of patients with neoplastic diseases

Normal distribution of data was assessed using the Shapiro–Wilk test. Pearson correlation was used to quantify the strength of the relationship between two continuous variables. Multivariate logistic regression models were created for multivariate analyses. Five-year overall and event-free survival were calculated. The multivariable Cox proportional hazard model was used to calculate the hazard ratio of OS and EFS. We estimated Kaplan–Meier survival curves and compared them with log-rank tests. Intercooled Stata version 10 (StataCorpLLC, TX, USA) was used for analysis, and $p < 0.05$ was considered significant.

IV.7. Applied statistical methods in the cross-sectional study of children with inflammatory bowel disease

Categorical variables between CD and UC patients were evaluated using chi-square or Fisher's exact test. The Kolgomorov-Smirnov test was used to examine the normal distribution of continuous variables. Quantitative variables were compared using the Kruskal-Wallis or Mann-Whitney test. Pearson correlation was performed to assess the relationship between nutritional status and activity index. A linear correlation analysis was performed to explore the interaction between nutritional status and disease activity. In addition, quadratic and cubic curve modeling and polynomial regression analysis were performed to characterize the nonlinear correlation between anthropometric data and disease activity. P values less than 0.05 were considered significant. The statistical analysis was made with the IBM SPSS Statistics 26.0.0.0 program.

V. RESULTS

V.1. Patient characteristics and follow-up in patients with leukemia and solid tumors

Among the 174 patients, there were 100 children with onco-hematological diseases (57.5%) and 74 with malignant solid tumors (42.5%). The median age at diagnosis was 7.34 years (range: 1.09–17.06 years). A total of 100 patients (57.5%) were boys. Finally, 137 patients (78.7%) were followed up until the end of therapy, two patients with hematologic neoplasia had an early relapse, and 15 died. Among patients with solid tumors, two early relapses occurred, six patients died during treatment, twelve suffered from progressive disease and did not reach remission. We lost a total of 33 patients during the anticancer treatment, and 36 patients during the five-year follow-up.

V.2. Nutritional status of patients at baseline and during follow-up

Average BW, WFH and BMI Z-scores were not significantly different from Z = 0, the average IBW% was above 90% examining patients' data at the time of diagnosis, which means, that the nutritional status of patients was adequate at the time of diagnosis. In general, the body weight of the patients decreased during the treatment, with average values decreasing significantly, and the nutritional status of the patients was worse at the second time-point of the study compared to the initial value (the time of diagnosis). By the end of treatment, body weight increased primarily in the group with malignant hematological diseases, meaning that the values were higher or similar compared to the baseline values. In the case of solid tumors, the rate of body weight gain was lower and less pronounced.

The proportion of undernourished patients at the three time-points of the study was as follows. IBW% indicated more undernourished patients than any other indicator at any time point. At diagnosis, 5.0%, 4.6%, and 4.0% of patients were undernourished based on BW, WFH, and BMI Z-score, respectively. When using IBW%, 30.5% of patients had an IBW% below 90%. This was observed in 26.0% of patients with hematological malignancies and 32.4% of patients with solid tumors.

During treatment, the body weight of patients decreased, and the proportion of undernourished children increased. IBW% appeared to be the most sensitive tool for assessing nutritional status. According to the IBW%, 57.00% of the patients became undernourished during treatment, 55.55% of the patients in the hematology group, while 59.10% of the children with solid tumors were undernourished. Considering the WL% exceeding 10%, 44.94% of the patients were undernourished. Examining the severity of undernutrition based on the percentage of weight loss, 31.10% of all patients were mildly and 12.90% moderately undernourished. Among patients with hematologic neoplasia, 32.90% of children were mildly and 11.30% moderately undernourished, while 28.50% and 15.00% of patients with solid tumors were mildly and moderately malnourished.

By the end of the treatment, the proportion of undernourished patients decreased in the group of patients with hematological malignancies based on IBW% (from 55.55% to 7.00%), whereas the other calculated parameters did not indicate undernutrition of patients. However, a significant number of children with solid tumors remained undernourished, as indicated by the Z-score values of BW, WFH, BMI, but mostly by IBW% (it decreased from 59.10% to only 36.20%).

V.3. Relationship between survival and nutritional status

Disease outcome and survival were greatly influenced by the nature of the malignancy. Twenty six percent of patients with malignant hematological diseases and 58% of patients with solid tumors died during or after treatment. According to our logistic regression analysis, the risk of mortality (odds ratio; OR) was 2.54 times higher in patients with solid tumors than in patients with hematological malignancies ($p < 0.001$, CI: 1.53-4.22).

The values of the anthropometric indicators (BW, WFH, BMI Z-score and IBW%) at the time of diagnosis were favorable based on the evaluation of all patients' data. The same can be experienced at the end of the treatment. In the case of good nutritional status, the risk of mortality was lower. However, when examining the survival probability of the group of patients with malignant hematological diseases based on the BW Z-score, if patients were classified into undernourished and adequately nourished groups, we found that the likelihood of survival decreased in the case of body weight below -2 Z-score. This effect on event-free survival was particularly evident.

Examining the probability of survival of patients with solid tumors, it could be established that BMI Z-score < -2 (HR: 4.54, 95% CI: 1.48-13.97, $p = 0.0081$) and IBW % < 90% calculated at the time of diagnosis (HR: 2.71, 95% CI: 1.45–5.07, $p = 0.002$) significantly impaired five-year OS.

The five-year OS and EFS determined by Cox regression analysis in the entire patient population showed that the lower the body weight and the calculated index during treatment, the higher the risk of death, relapse, or secondary malignancy in patients. The deterioration of the nutritional status resulting from the treatment adversely affected the OS in both patient groups. Abnormally low BW (HR: 7.2, 95% CI: 2.59–20.49, p <0.001), WFH (HR: 2.85, 95% CI: 1.1–7.38, p = 0.03) and BMI Z-score (HR: 5.98, 95% CI: 2.59–20.49 –16.74, p <0.001) showed a significant association with OS in the group of patients with hematologic neoplasia. In patients with solid tumors, WFH (HR: 2.67, 95% CI: 1.3–5.49, p <0.001) and BMI Z-score (HR: 2.47, 95% CI: 1.19–5.14, p = 0.015) showed similar results. IBW% had a significant effect on survival only in the group of patients with solid tumors (HR: 3.79, 95% CI: 1.25-8.24, p <0.001). Weight loss % adversely affected survival in both patient groups (HR: 4.13, 95% CI: 2.1-8.12, p <0.001). The risk of relapse or death was significantly higher in patients with hematological malignancies whose WL% exceeded 20% (HR: 5.34, 95% CI: 1.97-14.44, p <0.001). In contrast, moderate weight loss did not worsen EFS among patients with solid tumors (HR: 1.49, 95% CI: 0.59–3.72, p = 0.39).

Body weight measured at the end of the therapy and the anthropometric indicators calculated from it had no effect on survival in the entire study population, by this time the patients' body weight had increased, and the value of the calculated indices improved. BW, WFH and BMI had no effect on OS in the group of patients with hematologic neoplasia. Patients were no longer undernourished at this time, and survival was not affected by nutritional status at the end of therapy. In contrast, BMI status had a pronounced effect on the survival of patients with solid tumors at all times examined. The lower was the patient's body weight, and thus the BMI index calculated from it, the higher was the risk of death or relapse. The strongest and most significant association was found for EFS at the end of treatment (HR: 8.4, 95% CI: 1.77–40.52, p <0.001). All patients with solid tumors who remained severely undernourished based on BMI at the end of treatment had progressive disease and died.

V.4. Patient characteristics in children with Crohn's disease and ulcerative colitis

Six hundred and ninety-nine patients with CD and 328 with UC were included in the study. The median age at diagnosis in the CD group of patients was 14.4 years (mean 13.7 years, range 1.1-18.0 years). The mean age in the UC group of patients was 13.4 years (mean 12.7 years, range 1.6-18.0 years). Four hundred and seven (41.77%) patients with CD and 158 (48.17%) with UC were girls. According to the calculations of the disease activity index, 343 (50.66%) children suffered from mild, 152 (22.90%) moderately severe and 149 (22.00%) severe CD, 143 children (45.68%) had mild, 140 (44.72%) had moderately severe and 30 (9.60%) had severe UC.

V.5. Characterization of the nutritional status of patients with CD and UC

The nutritional status of most patients was adequate, regardless of the type of diagnosis and the examined anthropometric parameter. Both obese and undernourished patients represented a small population, there was no significant difference between the frequency of the two types of abnormal nutritional status. A higher proportion of patients with UC were obese when examined by any anthropometric parameter, but the difference was not significant compared to patients with CD. 2.71%, 2.28%, 2.69% and 7.02% of patients with CD were obese based on BW, BMI, WFH Z-score and IBW%, while in the UC group 6,48, 5.48%, 4.80% and 12.17% patients were obese according to the above indicators. IBW% identified 2-3 times more obese patients than any other parameter in both groups. At the other end of the nutritional status spectrum, more patients with CD were undernourished than patients with UC by any of the investigated parameters, but the difference was not significant between the two patient groups.

V.6. Correlation between differences in nutritional status and disease activity

The median PCDAI value of patients with CD was 30 (mean: 30.60±15.03; range: 0-87.5), the median PUCAI value of patients with UC was 35 (mean 38.56±19.02; range 5-85). Analyzing disease activity in groups of patients with different nutritional status determined by BW, WFH, BMI Z-score and IBW%, we found that PCDAI was significantly higher among undernourished than among well-nourished and obese patients with CD regardless of the applied anthropometric parameter. PCDAI showed a further significant decrease in obese patients compared to well-nourished patients.

On the other hand, in the group of patients with UC, only the estimates based on WFH and BMI determination showed a significant difference between the disease activity indicators of the subgroups according to the nutritional status. Similar to patients with CD, undernourished patients had significantly higher disease activity than well-nourished or obese patients. We did not observe a significant difference in PUCAI between well-nourished and obese patients.

Using linear regression analysis, we found no significant correlation between anthropometric results and activity indices (disease activity) either in CD or in UC groups of patients. Our results indicated a more complex relationship between activity indices and nutritional status, so we divided the entire population of patients with CD and UC into two groups. The groups below and above the median value of the investigated anthropometric indicators were re-analyzed separately, using linear regression analysis. We found a significant negative correlation between certain anthropometric indicators of “below the median“ anthropometric values and disease activity in patients with CD. Worse nutritional status was associated with more severe disease activity (BW Z-score R: -0.148, B:-7.440, p:0.006, WFH Z-score R:-0.221, B:-7.080, p:0.000, BMI Z-score R:-0.314, B:-10.745, p:0.000, IBW% R:-0.194, B:-0.465, p:0.000). On the other hand, no significant correlation was found among patients with CD characterized by anthropometric parameters exceeding the median value.

In the group of “below the median” group of patients with UC, only the WFH Z-score (R-0.196, B: -6.955, p:0.002) and the IBW% (R: -0.174, B: -0.537, p: 0.033) reproduced the same significantly negative correlation in association with disease activity, similar to patients with CD. In the subgroup of “above the median IBW%” group of patients with UC an opposite, significantly positive correlation (R:0.166, B:0.171, p:0.044) was observed with the activity of the disease, which indicated a relationship between disease activity and nutritional status that can be described by a U-shaped correlation curve.

To refine the investigation between the relationship of disease activity and nutritional status, we performed additional polynomial regression analysis. In patients with CD, all examined parameters showed a decreasing, significant cubic correlation (sigma-shaped curve) with disease activity, where R values were 0.22, 0.22, 0.22, 0.23 (p<0.000) according to BW, WFH, BMI and IBW%.

On the other hand, in the entire group of patients with UC, a typical U-shaped curve was obtained by examining the relationship between PUCAI and nutritional status by quadratic analysis. All the anthropometric parameters, such as BW, expected WFH, BMI and IBW% were significantly correlated with disease activity, R value 0.16 (p=0.019), 0.19 (p=0.004), 0.2 (p=0.019) and 0.19 (p=0.006), respectively. These results assumed a bimodal effect of nutritional status between disease activity and anthropometric indicators in patients with UC. Deviations from optimal anthropometric values in both negative and positive directions (undernutrition and obesity) had a negative effect on disease activity.

VI. DISCUSSION

The present epidemiological studies conducted among children with cancer and IBD are the first in our country to assess the nutritional status of these patients. In the case of children suffering from cancer, the study focused primarily on weight loss during treatment and its negative impact on survival. In children with IBD, weight loss, especially at the time of diagnosis, is a well-known clinical symptom. Less attention is paid, however, worldwide to obesity and its potential impact on disease activity, even though obesity is perhaps one of the most threatening public diseases in the modern world. To assess and monitor the nutritional status, the literature and scientific societies mostly recommend the calculation and monitoring of the BMI Z-score. In the present study we wanted to focus on additional anthropometric indicators of nutritional status, including IBW%, and WL% which are not routinely used, but may help in characterizing the nutritional status of patients and their prognosis more precisely. The present results confirmed our hypothesis in both study groups, according to which both IBW% presented as the ratio of actual body weight to the expected body weight for height and WL% are useful anthropometric indicators in assessing nutritional status of children with cancer or inflammatory bowel disease.

VI.1. Assessment of the nutritional status of cancer patients

Frequency of undernutrition at the time of diagnosis was 4-5% of children suffering from malignant hematological diseases and solid tumors, based on classical anthropometric indicators. In contrast, prevalence of undernutrition defined by IBW % (<90%) was 30%. During anticancer management, due to side effects of treatment and other known iatrogenic factors (such as tasteless hospital food, missed meals, starvation before surgery, bad eating habits, etc.) and the underlying disease, nutritional status of patients deteriorated, their body weight decreased, and the rate of undernutrition increased 2 to 3 times (depending on the used anthropometric parameter). Undernutrition is a common complication of childhood cancer; its prevalence varies between 5-60% worldwide. Our results based on BMI Z-score determination are similar to the data of the reports of developed countries with high GDP. In a Dutch survey, patients became undernourished at a similar rate as in our country, while in a Swiss survey, 41-47% of the patients became undernourished determined by the same anthropometric parameter. Based on BMI Z-score, undernutrition occurred in 11.1% of patients with malignant hematological diseases and 26.5% in patients with solid tumors. By the end of the anticancer therapy, the nutritional status of our patients improved, based on weight gain, resulting, consequently, in the improvement of the derived anthropometric parameters.

A similar proportion of patients proved to be undernourished at any time of the study, if the nutritional status was determined by BW, WFH and BMI Z-score. Opposite to results above, IBW% indicated undernutrition to a significantly greater extent compared to indicators generally recommended for patient follow-up. The difference was sixfold at the time of diagnosis, and fourfold during treatment and at the end of treatment. A similar result to IBW% was obtained by calculating WL%. According to this indicator, 44.94% of patients were undernourished, while 57% of patients were undernourished based on IBW%. The importance of this observation: if the child's body weight was optimal or overweight at the time of diagnosis, and height growth may slow down, then the BW, WFH and BMI Z-score may decrease during treatment but will not necessarily become pathologically low and the patient will not be considered undernourished by definition. Weight loss is a clear indicator of insufficient caloric intake, starvation, and malnutrition. Calculation of IBW% and following changes in this indicator during treatment clearly draws attention to the presence of protein- and energy deficiency malnutrition.

Among patients with solid tumors, due to the limited data available, we assessed the nutritional status of the child only at the time of diagnosis. It is a well-known fact that loss of body weight and growth retardation in childhood can be a symptom of cancer. This process can start in parallel with the development of the tumor, whereas the presence of the tumor can be diagnosed weeks or even months later compared to the actual development of the disease. Previous weight loss is registered regularly in adult patients with cancer, unfortunately however, this important part of patient history receives less attention in pediatric oncology centers. Therefore, we could not investigate the impact of possible weight loss before establishing the diagnosis. Consequently, our results do not always show the real pre-cancer nutritional status of the child. Therefore, the survival results based on anthropometric parameters calculated before the diagnosis of cancer has been ascertained, may alter the influence of the nutritional status on treatment outcome, as compared to the prediction based on parameters obtained at diagnosis.

Survival of children with cancer is influenced by the type of the underlying disease. In the present patient group, the risk of mortality in solid tumor was 2.54 times higher than in the case of oncohematological diseases. The lower body weight, the calculated BMI Z-score, and IBW% at the time of diagnosis in patients with solid tumors had a negative effect on overall and event-free survival. Body weight loss during treatment deteriorated survival in both patient groups. The greater was the child's weight loss, the greater was the risk of mortality. This relationship was observed most clearly when we investigated EFS of patients with malignant hematological diseases, whose body weight loss exceeded 20%. The risk of relapse or death was 5.34 times higher compared to those who did not lose that much percent of their body weight. Reviewing the data of these patients, we found that most of them had acute lymphoblastic leukemia, and 5 of the 49 ALL patients died during treatment. Today, especially in patients with high-risk ALL, infections and treatment-related mortality are the most important factors influencing survival, and undernutrition has much lesser importance in this respect. However, undernutrition increases the risk of developing infections and side effects associated with treatment. Western European studies reported a lower rate of undernutrition during anticancer treatment and weight gain experienced at the end of the treatment compared to our study. Based on the available data, we cannot explain why the phenomenon of weight loss was more common in the study cohort, but we must assume that during the study period, especially during its first phase, our nutritional support practice was less rigorous than in Western European centers.

Children with solid tumors had worse survival probability than children with malignant hematologic diseases. In addition to their illness, the probability of survival was reduced by undernutrition that persisted by the end of the treatment. Low BMI Z-score, calculated at the end of treatment (poor nutritional status) increased the risk of mortality and relapse by 8.4 times in patients with progressive disease.

Our results provided information about the nutritional status of children living in North-East Hungary and receiving active anticancer treatment. Rate of undernutrition at the time of diagnosis did not differ from the prevalence data of Western European countries with high GDP and developed health systems. Good nutritional status at the time of diagnosis reduced the risk of mortality and morbidity. However, the survival rates of our patients lag Western European and North American results. This unfavorable fact may be the consequence of the (high) degree of weight loss and the (high) rate of undernutrition during the treatment, which exceeded the level observed in Western Europe and North America.

Our study draws attention to the fact that monitoring the nutritional status of patients, preventing weight loss, and providing adequate caloric intake for patients are essential parts of care. According to our data, the early detection of undernutrition is mainly possible by the determination of IBW% presented as the ratio of actual body weight to the expected body weight for height, therefore, it is recommended to determine and to follow this index in addition to the BMI Z-score in children with cancer. Calculating WL% offers similar benefits. In case of weight loss exceeding 10%, further weight loss can be prevented with early feeding therapy, thereby increasing the possibility of survival. The limitation of our retrospective study is the small number of cases, so we did not have the opportunity to examine the relationship between undernutrition and survival in different disease groups, or to compare the diseases with each other. Due to the retrospective nature, we also did not have the opportunity to map what exactly caused the patients' death or weight loss, especially in children treated with ALL. Undernutrition has not been considered as one of the prognostic factors of childhood ALL. Further investigations are required if preventing weight loss or achieving weight gain might have a beneficial effect on survival.

The consequences of malnutrition and inadequate support or nutrition (enteral and parenteral) are important aspects of supportive care, which unfortunately have been too frequently neglected due to the focus on anticancer treatment. These findings, together with similar observations from more Hungarian pediatric cancer treatment centers, prompted us to prepare guidance for nutritional support of children during anticancer management. Results of the introduction of this guidance have not been reflected, however, in this retrospective cohort. In recent years several important results have come to light about the importance of body composition analyzes during anticancer treatment. This encourage us to use modern methods that are available in our center (BIA) or become available to childhood patients with acquisition of software and practice also (DEXA, CT, MRI) in addition to anthropometric methods. Knowledge of muscle mass and fat mass creates an opportunity to plan individual, patient-oriented nutrition therapy, and at the same time to rehabilitate the patient.

VI.2. Nutritional status and childhood inflammatory bowel disease

Undernutrition among patients with IBD is a common phenomenon in both children and adults before and after diagnosis, especially among patients with CD. In the recommendations for the treatment of IBD, great attention have been paid to the elimination of states of deficiencies and to the optimal nutritional therapy. In childhood CD, exclusive enteral nutrition has become an accepted therapeutic modality for induction of remission, which can cure the pathologic mucous membrane (mucosal healing). In addition, it also has a steroid-saving effect, since its remission efficiency is the same as that of corticosteroids. In some cases, this drug, with a widespread side effect profile (such as, excessive weight gain, hypertension, depression, elevated blood glucose level, immunosuppression, etc.), can be omitted from the treatment. In addition, the nutritional status of undernourished patients can be improved by consuming the formula in the proper amount.

The level of undernutrition was not high among Hungarian children diagnosed with IBD between 2010 and 2016, based on the results of the first epidemiological study on nutritional status. Two-point-seven % of patients with CD and 1.83% with UC proved to be undernourished examined by BMI Z-score. Comparing our results with data from North American and European countries, the prevalence of undernutrition is clearly lower in our country among children with IBD. Similarly, few children were found to be overweight or obese examined by BMI Z-score applied according to recommendations of international gastroenterology societies. The proportion of obese children was almost like the results of the survey conducted in the general Hungarian child population. As much as 2.28 % of patients with CD and 5.45% with UC were obese, their BMI Z-score exceeded 2.

Using the IBW% calculation, which proved to be useful among patients with cancer, both undernutrition and obesity became detectable at a higher rate at the time of diagnosis, when the children had not yet received medication, such as corticosteroid treatment. Among patients with CD, IBW% was lower than 90% in half of the examined population (50.45%), while the rate was ~~in~~ 33.67% among patients with UC. Obesity was present in 7.02% of patients with CD and 12.17% of patients with UC. The higher proportion of obese children in the UC group of patients, compared to CD is typical not only in our country, but also in pediatric patients from other nations.

Since undernutrition is well known in childhood IBD, we focused our attention to the presence and impact of obesity. The public health importance of obesity is unquestionable. It has also fact been suggested that, in addition to genetic and environmental factors and changes in the intestinal microflora, obesity may play a role in the development of IBD. Adult epidemiological studies suggested that obesity increased the risk of developing CD among young North American women. Studies on the relationship between obesity and IBD conducted in the pediatric population focused primarily on the prevalence of obesity. These surveys found obesity more common in patients with UC than with CD.

The activity of IBD can be assessed most simply by calculating activity indices (PUCAI, PCDAI) without the use of invasive methods. We found that activity index of undernourished children in CD is higher, than among properly fed and obese patients at the time of diagnosis. PCDAI gradually decreased with increasing body weight. In contrast, both undernourished and obese children in UC had higher PUCAI values. Based on the results of polynomial regression analysis, we were the first to report that there may be a correlation between obesity determined by anthropometric methods and childhood UC activity, raising the possibility that obesity has a negative effect on disease activity. The association proved particularly robust when nutritional status was defined by IBW%.

Our results support the theory that obesity, a proinflammatory state, may contribute to increased disease activity in UC. Moreover, obesity can be a risk factor in the development of childhood UC, like in rheumatoid arthritis.

The results of the present study are limited by the fact that we did not perform an accurate body composition analysis. It is known that the most accepted anthropometric indicator of obesity is BMI. In the case of obesity, the excessive accumulation of fat tissue is typical for the increase in body weight, however, the increase in body weight and thus the increase in the BMI value can also be caused by an increase in muscle mass in persons in whom the accumulation of fat tissue is not present (e.g., bodybuilders). Since we have no data on the amount and distribution ratio of fat-free body mass and adipose tissue in the studied population, we can only assume that the higher BMI and IBW% were due, indeed, to the accumulation of adipose tissue with inflammatory activity. In addition, we have no information about the presence and amount of viscerally located mesenteric, hormonally active adipose tissue that crawls up the intestinal wall, which is primarily a characteristic entity in CD and is characterized by proinflammatory cytokine production, similarly to the visibly present excessive adipose tissue. Another limitation of our study is that we do not have data on the patients' dietary habits, such as consumption of refined sugar, and fat. Their excessive intake and the continuation of a Western-style diet are one of the most important environmental etiological factors of IBD. The same dietary habits are also responsible for the development of obesity.

The change in the diversity of the intestinal flora, its role in the development of inflammatory phenomena and obesity became the focus of research. Changes in the composition of the intestinal flora are known in IBD, but for now we do not know whether the imbalance of the microbiome results in intestinal inflammation or obesity. Further studies, investigating the interactions between the intestinal microbiome, the altered anti- and proinflammatory balance, and obesity may answer the question if obesity can be considered a risk factor for the development of childhood UC.

Primary goal of our study was to assess the prevalence of obesity and the effect of its disease activity, but we cannot go without saying that not only the excessive accumulation of adipose tissue, but also the early detection and possibly reduction its amount may also become part of the treatment protocol for children with inflammatory bowel disease in the future. Accurate analysis of the patient's fat and fat-free body mass is also necessary due to sarcopenic obesity, which does not manifest itself as an increase in body weight but can be suspected with a thorough physical examination. Knowing the ratio of body composition can create an opportunity to plan nutrition therapy for inflammatory bowel disease in the form of increased protein and reduced carbohydrate intake, supplemented by increased physical activity and rehabilitation of the child. Similar to the body composition analysis options mentioned in our center for cancer, it is worth using them in children treated for IBD (DEXA, CT, MRI, BIA). Further prospective studies are needed to investigate the role of obesity in de novo IBD and the outcome of the disease by determining body composition and examining pro- and anti-inflammatory cytokines and adiponectins.

VII. NEW FINDINGS

1. The frequency of undernutrition among children suffering from cancer in the region of North-East Hungary is the same as the prevalence data of Western Europe and North America, countries with developed health systems and high GDP.
2. Using IBW% presented as the ratio of actual body weight to the expected weight to height, which is rarely recommended by international guidelines for assessing nutritional status, a higher proportion of undernourished children with cancer can be detected. By using IBW% and WL% in everyday patient care, it is possible to detect body weight loss that adversely affects survival, as soon as possible, thereby starting supportive nutrition therapy.
3. Among children with hematologic malignancies who were well-nourished at the time of diagnosis, the factor influencing mostly the risk of mortality and the probability of survival is weight loss during treatment. The mortality of children with hematological diseases who lost more than 20% of their body weight and otherwise have good survival chances, was significantly increased.
4. The prevalence of undernutrition among Hungarian children with IBD is lower than in Western Europe and North America. Obesity, on the other hand, occurs with a similar frequency. The incidence of obesity among patients with IBD was not more frequent than in the average domestic population.
5. The disease activity index determined at the time of diagnosis indicated moderately severe or severe disease in both undernourished and obese patients with UC. The relationship was strongest when nutritional status was determined by IBW%. The calculation of IBW% ~~is~~ can be considered a sensitive method for assessing nutritional status not only in children with cancer, but also in children with IBD.
6. Moderate to severe disease activity observed in undernourished and obese patients with UC at the time of diagnosis suggested a bimodal effect of nutritional status on disease activity. According to the results, the disease activity was not only high in undernourished patients, but it was also associated with obesity present at the time of diagnosis. This finding is the first in the international literature.

VIII. SUMMARY

Maintaining and preserving the appropriate nutritional status for a developing and constantly growing healthy or sick child is one of the most important tasks in pediatrics. Deterioration of nutritional status and the development of undernutrition are well-known complications of cancer. Malnutrition adversely affects morbidity and mortality and impairs the patient's quality of life. The incidence of childhood cancer is high worldwide and malignant diseases represent the leading cause of death in developed countries after accidents. The prevalence of IBD is gradually increasing, with a quarter of patients being diagnosed in adolescence. In the case of IBD, the basic social problem is not the high mortality, but the associated diseases and complications, the heavy financial burden on the health care systems, and the decreasing contribution of patients to the social system. The patients' quality of life is primarily determined by the activity of their disease. Disease activity can be worsened by poor nutritional status, whether it is undernutrition or overweight. In the case of IBD, the proinflammatory effect of obesity can even aggravate the patient's complaints and disease activity. Moreover, diseases associated with obesity can further deteriorate the quality of life of patients and make medical treatment more difficult.

In course of the present investigations, we determined the nutritional status of children with cancer and IBD. We used anthropometric methods that are easily available and feasible in everyday practice. In addition to the anthropometric indicators for assessing nutritional status (BW, WFH, BMI Z-score) recommended by societies of pediatric oncology and gastroenterology (SIOP, ESPGHAN), we also performed calculations with parameters that are less common in practice, but which clearly indicate changes in nutritional status caused by protein-, energy deficiency (IBW%, F%).

Our results confirmed the adverse effect of undernutrition on survival in children with cancer, especially when nutritional status was assessed by IBW% presented as the ratio of actual body weight to the expected weight to height and WL%. With the early recognition of undernutrition and the introduction of supportive nutrition therapy, the chances of patients for survival can be improved. In the overburdened domestic healthcare system, it is a desirable goal that all of healthcare providers, involved in patient's care, can follow changes in the nutritional status using the simplest method. Following changes in body weight and body height and determining the percentage of body weight loss seems to be a reasonable method even in the absence of tools for accurate body composition measurement (e.g., bioelectrical impedance analysis). As undernutrition is closely related to survival, our data support the importance of close monitoring of nutritional status in children with malignancy.

Undernutrition and obesity are not more common among Hungarian children suffering from IBD than among their healthy peers. However, obesity, especially when assessed by IBW%, proved to be an important risk factor for UC disease activity in the Hungarian pediatric population. This study revealed that IBW% previously used among cancer patients is a valuable method for assessing nutritional status in children with IBD and identified more patients with inadequate nutritional status than BMI Z-score. Considering that not only undernutrition, but also obesity adversely affected the disease activity of IBD in patients diagnosed with UC, it is essential to recognize overweight in children as soon as possible and take preventive measures in the direction of weight reduction.

XI. KEYWORDS

- nutrition, cancer, pediatric, survival, weight loss
- obesity, inflammatory bowel disease, children, disease activity index, Crohn's disease, ulcerative colitis

IX. LIST OF PUBLICATIONS

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List of publications related to the dissertation

1. **Kadenczki, O.**, Dezsőfi, A., Cseh, Á., Szűcs, D., Vass, N., Nemes, É., Tárnok, A., Szakos, E., Guthy, I., Kovács, M., Karoliny, A., Czelecz, J., Kiss, C., Müller, K. E.: Disease Activity Is Associated with Obesity in Newly Diagnosed Pediatric Patients with Ulcerative Colitis. *Int. J. Environ. Res. Public Health. 19*, 1-12, 2022.

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