BODY MUSCLE MASS METABOLIC DATA ANALYSIS IN ASSOCIATION WITH CROHN'S DISEASE ACTIVITY

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Malnutrition is a common complication of Crohn's disease (CD) patients and it is correlated with alterations of the body composition and disease activity. Our prospective pilot study included hospitalised CD patients, age ≥ 18 years. Patients were assessed using the Nutritional Risk Score (NRS2002), the Malnutrition Universal Screening Tool (MUST), and body bioelectrical impedance analysis. Twenty-three hospitalised patients (median age 36.5, interquartile range (IQR): 28.5–51.5 years) were enrolled; the median CD activity index was 128 (IQR = 6.0–207.0). The study group comprised 48% ($n = 11$) patients with low CD activity and 52% ($n = 12$) with high disease activity. According to NRS2002 and MUST, 70% ($n = 16$) CD patients had malnutrition risk and were in need of nutritional support. The median BMI was lower for the CD group (21.10 [IQR = 19.2–23.3]) than for the control group (23.4 [IQR = 21.5–25.8]) ($p = 0.014$). In terms of deviation from standard weight, 39% ($n = 9$) of CD patients showed reduced % body fat. Reduced muscle mass was observed in 48% ($n = 11$) of CD patients. CD patients with high disease activity had a noticeably increased risk of malnutrition. Identification of the reduction in soft lean muscle mass in CD patients can be used as an anticipatory indicator of disease activity.

Keywords: inflammatory bowel disease, Crohn's disease activity index, malnutrition, screening tools.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with periods of activity and remission (Ferre *et al.*, 2018). In industrialised countries, IBD has become a global disease and the incidence of CD has risen significantly over the past half century (Levine *et al.*, 2020). The highest reported prevalence values were in Europe — 322 cases per 100 000 (Ng, 2017). Smoking, use of antibiotics, and diet are potentially preventable risk factors for IBD (Forbes *et al.*, 2017). CD commonly can lead to malnutrition, estimated in 65–75% of patients with CD (Scaldaferri *et al.*, 2017), and specific nutritional deficiencies, which may be caused by low dietary intake, changes in metabolism, increased intestinal protein loss, and nutrient malabsorption (Jahnsen *et al.*, 2003; Wędrychowicz *et al.*, 2016). The nutritional status of IBD patients is frequently altered,

even when the disease is in remission, although it is directly related to the severity of the disease (Back *et al.*, 2017; Casanova *et al.*, 2017).

Malnutrition is an objective disease activity parameter for patients with IBD, particularly CD, and is an indicator of systemic damage or inflammatory activity. Active disease is correlated with the systemic response of the body's immune system, activating a hypermetabolic state and protein degradation, decreasing protein synthesis (Argiles *et al.*, 2015). These conditions lead to malnutrition, which significantly increases the risk of impaired clinical outcomes, such as delayed recovery or increased mortality (Landi *et al.*, 2019). Inadequate body composition and malnutrition have been associated with poor outcomes, such as a higher frequency of postoperative complications, longer hospital stays, decreased quality of life and higher health costs (Casanova *et*

et al., 2017). The severity of malnutrition depends on the activity, duration and extent of the disease, and inflammatory response, which drives catabolism (Forbes *et al.*, 2017).

To evaluate malnutrition, basic anthropometry techniques were used, such as body mass index (BMI) and biochemical parameters, but they are not accurate enough to estimate body composition. In a high proportion of IBD patients, these values may be within normal ranges, while they still have an altered body composition. Therefore, bioelectrical impedance analysis (BIA) is used to calculate total body water (TBW), and to estimate fat-free mass (FFM) [lean mass], muscle and fat mass (Casanova *et al.*, 2017). BIA is easy, non-invasive, relatively inexpensive and can be performed in almost any subject because it is portable (Kyle, *et al.*, 2004). Screening for malnutrition, using screening tools like the Nutritional Risk Screening Score 2002 (NRS2002) and Malnutrition Universal Screening Tool (MUST), which are recommended by the European Society of Clinical Nutrition and Metabolism, is important to identify subjects at nutritional risk (Kondrup *et al.*, 2003). Referring to recommendations, screening should be performed within the first 24–48 h after first contact and thereafter at regular intervals. For those identified as being at risk by nutritional screening, nutritional assessment should be provided (Caderholm *et al.*, 2017).

Recent studies have shown that between 22% and 60% of patients with IBD have FFM depletion. This is significant because FFM depletion has been associated with negative outcomes, including major postoperative complications predicting a small bowel resection, primary non-response to antitumor necrosis factor (TNF) agents, and osteopenia. Traditional nutritional measurements, like BMI, correlate poorly with indices of FFM in patients with CD, resulting in a risk for under recognition and underestimation of the extent of nutrition depletion when relying only on weight-based indicators of nutritional status (Wood, 2020). Reduced muscle mass has been included in the Global Consensus for Diagnosing Malnutrition in Adult Patients (Cederholm *et al.*, 2019).

The aim of this study was to analyse body muscle mass metabolic data in association with Crohn's disease, identifying patients with low and high disease clinical activity.

MATERIALS AND METHODS

This prospective pilot study included twenty-three hospitalised patients aged ≥ 18 years, with an established diagnosis of CD and no medical history of surgical interventions. CD patients were divided into those with low and high clinical activity indexes, according to the CD activity index (CDAI): low clinical activity index (CDAI < 150) and high clinical activity index (CDAI > 150).

Patients were assessed twice using the Nutritional Risk Score (NRS2002) and Malnutrition Universal Screening Tool (MUST), recommended by the European Society of

Clinical Nutrition and Metabolism. The MUST has been found to have excellent inter-rater reliability, concurrent validity with other tools, and predictive validity (length of hospital stay and mortality). Its purpose is to identify individuals at risk of developing malnutrition based on nutrition status (BMI and weight loss) and disease-related dysfunction. NRS2002 contains the nutritional components of MUST, and in addition, a grading of severity of disease as a reflection of increased nutritional requirements; its purpose is to identify patients at risk of malnutrition within 48 hours after hospital admission and to determine those who would benefit from early nutrition therapy (Kondrup *et al.*, 2003; Rabito *et al.*, 2017).

Body bioelectrical impedance analysis (BIA) measurements were performed using impedance equipment at least three hours after eating, as this may reduce small errors in impedance determination (Kyle *et al.*, 2004). The whole body was measured, by subdividing it into various segments. Furthermore, weight (kg), BMI, fat-free mass (FFM) (kg), soft lean mass (SLM) (kg), metabolic body fat (MBF) (kg), total body water (TBW) (kg), basal metabolic rate (kcal), total energy expenditure (kcal), visceral fat (%), and per cent body fat (PBF) were assessed.

A control group consisting of twenty-three healthy age- and sex-matched individuals was used for comparison. BIA was performed if the person met the inclusion criteria: age ≥ 18 years old and age-matched to the patient group, with no food intake ≥ 3 hours prior to testing, and with no nutritional risks identified using both screening tools (NRS2002 and MUST), which assured that the control group did not harbour any active disease that would interfere with the study results.

Statistical analysis was performed using SPSS version 22 (IMDB Statistical Package for the Social Sciences 22). Statistical significance was set at p -values ≤ 0.05 . The study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee.

RESULTS

Twenty-three hospitalised patients (median age 36.5, interquartile range (IQR): 28.5–51.5 years) were enrolled, 39% ($n = 9$) were female and 61% ($n = 14$) male. The median CDAI was 128 (IQR = 6.0–207.0). The study group comprised 48% ($n = 11$) patients with low CD activity and 52% ($n = 12$) of patients with high disease activity (Fig. 1).

According to NRS2002 and MUST, 70% ($n = 16$) CD patients were nutritionally at risk and in need of nutritional support. From twelve patients with high disease activity, 92% ($n = 11$) had a risk of malnutrition, and from eleven patients with low disease activity, only 45% ($n = 5$) has a risk of malnutrition ($p = 0.027$). Clinical nutrition was administered to 11 patients; enteral oral feeding was prescribed to nine of these patients. Additionally, two patients received parenteral peripheral feeding.

Fig. 1. Diagram of study flow.

Table 1. Comparison of parameters between Crohn's disease patients and the control group

Parameters	CD patients	Control group	p-value
Weight (kg)	68.7 ± 14.8	73.5 ± 13.9	0.232
PBF (%)	21.3 ± 7.5	21.8 ± 9.9	0.355
Muscle mass deviation from normal	0.6 ± 3.1	2.9 ± 4.6	0.143
Fat deviation from normal	1.3 ± 6.8	1.8 ± 5.0	0.122
Muscle mass	49.6 [41.1–57.3]	55.8 [42.9–61.4]	0.425
Proteins	38.7 [32.2–44.4]	12.5 [9.6–13.8]	< 0.001
Minerals	3.8 [3.4–4.7]	4.3 [3.6–4.7]	0.212
TBW	38.7 [32.20–44.35]	43.1 [33.4–47.4]	0.454
Basal metabolism	1503.0 [1196.00–1607.0]	1518.5 [1266.5–1711.8]	0.407
Weight deviation from normal	4.1 [–8.4–6.3]	4.2 [–1.2–12.2]	0.102
BMI	23.4 [19.2–23.3]	21.1 [21.5–25.8]	0.014
Visceral fat %	–4.0 [–12.1–5.6]	7.9 [–0.9–18.2]	0.003

BMI, body mass index; CD, Crohn's Disease; PBF, percent body fat; TBW, total body water

Data obtained by BIA was compared between the study group to those of the population control group (Table 1). Statistically important differences were observed in BMI, % visceral fat and proteins. Other values also seemed to vary, but analysis did not show statistically significant differences. The albumin level was determined for 17 patients, of whom 24% (n = 4) had a reduced albumin level (< 3.5 g/dl) at the moment of admission.

Comparing BIA results between CD patients and the control group, the median BMI was significantly lower for the CD (21.10 [IQR = 19.2–23.3]) than for the control group (23.4 [IQR = 21.5–25.8]) ($p = 0.014$). In addition, visceral fat mass was significantly lower in the CD (–4.00 [IQR = –12.1 to 5.6]) than in the control group (7.85 [IQR = –0.9–18.2]) ($p = 0.003$). An imbalanced body composition with changes in PBF and SLM was observed in a large proportion of patients. In terms of deviation from standard weight, 39% (n = 9) of CD patients showed reduced PBF. This indicated that even though patients had BMI within normal values, there was a high chance of having imbalance in body composition. Reduced muscle mass was observed in 48% (n = 11) of CD patients. CD patients were more prone to reduction in muscle mass when disease activity is high. Only a few individuals of the control group had muscle mass under the normal values.

DISCUSSION

In our study, according to NRS2002 and MUST, 70% CD patients were nutritionally at risk and in need of nutritional support. In a previous study (Stratton *et al.*, 2004) using MUST, the prevalence of malnutrition risk ranged from 19–60% in inpatients and 30% in outpatients. Our results were higher, which can be explained by higher disease activity and probably with various nutritional and metabolic disturbances. Our data indicated strong agreement between both scales on evaluation of the nutritional status of the patient. Similar agreement has also been reported (Stratton *et al.*, 2004), where MUST had excellent agreement (k 0.775–0.893) with MEREC, NRS and SGA tools).

Those identified to be at risk of malnutrition by using malnutrition screening tools, should be followed by nutritional assessment, which will give the basis for the diagnosis, as well as for further action including nutritional treatment. Assessment of the nutritional status integrates information on body weight, body height, body mass index (kg/m^2), body composition and biochemical indices (Cederholm *et al.*, 2017).

Malnutrition is defined as a subacute or chronic state in which a combination of negative energy balance and varying degrees of inflammatory activity has led to changed

body composition, diminished function, and adverse outcomes (Cederholm *et al.*, 2017). Malnutrition adversely affects physical and psychological function and impairs a patient's recovery from disease and injury, thereby increasing morbidity and mortality. Despite being a common problem, malnutrition is frequently unrecognised and untreated in many health care settings, including nursing and other care homes, general practice, and hospital outpatients and inpatients (Stratton *et al.*, 2004).

It has been reported that ileal involvement in CD patients plays a relevant role in reducing nutrient absorption (Balestrieri *et al.*, 2020). Nutritional deficiencies are self-evidently more likely in patients with CD affecting the small bowel than in those with isolated colonic disease (Forbes *et al.*, 2017).

The severity of malnutrition is dependent on the activity, duration, and extent of the disease and, in particular, on the magnitude of the inflammatory systemic response mediated by pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α and interleukins-1 and -6, which can increase catabolism and lead to anorexia (Balestrieri *et al.*, 2020). In our study it was confirmed that patients with higher disease activity have a higher risk of malnutrition. From twelve patients with high disease activity, 92% ($n = 11$) had a risk of malnutrition, and from eleven patients with low disease activity, only 45% ($n = 5$) had a risk of malnutrition. This difference was statistically significant ($p = 0.027$).

Detection of reduced body muscle mass has emerged as a crucial variable in nutritional assessment. A progressive and general loss of lean muscle mass associated with decreased muscle strength or physical performance has significant impact on the quality of life and causes physical disability (Balestrieri *et al.*, 2020). A systematic review (Ryan *et al.*, 2019) reported that up to 60% IBD patients have decreased muscle mass when compared with healthy subjects and a higher percentage were patients with CD and these patients were more likely to be male (Ryan *et al.*, 2019). In our study, reduced muscle mass was observed in 48% of CD patients and 39% were men. Low lean mass is likely a surrogate marker of ill-health and inadequately controlled disease activity, and may be associated with fatigue and reduced quality of life in patients with IBD. Some studies have shown that BMI does not correlate well with lean mass in patients with IBD, even amongst those in clinical remission. Increase of BMI may be related to gain in fat mass, further masking the underlying lean mass deficit. BMI was shown to better correlate with fat mass than with lean mass. In fact, a normal BMI was falsely reassuring in 72% of patients who were demonstrated to have low lean mass (Bryant *et al.*, 2015).

According to the World Health Organisation standardised criteria, patients were considered to be well-nourished when their BMI was between 18.5 and 24.5 kg/m², underweight or malnourished when their BMI was ≤ 18.5 kg/m², and overweight when their BMI was ≥ 25 kg/m². According to our results, BMI was decreased only in three patients. There-

fore, the evaluation of BIA parameters is important. Evidence shows that reduced muscle mass can also be related to an unchanged or even elevated BMI (Balestrieri *et al.*, 2020). Therefore, it is important to assess those who are not visibly malnourished.

In systematic review (Ryan *et al.*, 2019), it was reported that the serum albumin concentration was significantly lower in patients with CD compared with controls (2.6 g/dl vs 3.0 g/dl; $p = 0.002$). In another review (Zhang *et al.*, 2017) the estimated mean albumin concentration for patients at high risk of malnutrition (detected by NRS-2002) was 3.42 (95% CI: 3.19, 3.64). This indicates that using albumin with a cut-off of 3.5 g/dl would fail to identify a proportion of the patients diagnosed to be at high risk of malnutrition using NRS-2002, not to mention those at low malnutrition risk. In our study, from seventeen patients for whom the albumin level was determined, only four patients had a reduced albumin level (< 3.5 g/dl). Therefore, the significance of serum albumin as an indicator of nutritional status is controversial, because the serum albumin level is affected by intravenous fluids and dehydration (Takaoka *et al.*, 2018).

Monitoring of anthropometry provides insight into which patients develop relative deficits in lean mass and therefore would benefit from nutritional supplementation. The protein requirement is increased in active disease, and intake should be increased, but in remission the protein requirements are generally not elevated and provision should be similar to that recommended in the general population. In general, no specific diet needs to be followed during remission phases (Forbes *et al.*, 2017).

Nutrition or nutrients can be provided orally, via enteral tube-feeding or as parenteral nutrition to prevent or treat malnutrition in an individualised way (Cederholm *et al.*, 2017). The nutritional care plan is based on the results of the assessment. This plan should be developed by a multi/interdisciplinary team together with the patient. In our study, nine patients received enteral and two patients parenteral feeding that was individualised for each patient based on nutritional assessment results.

CONCLUSION

CD patients with high disease activity had a noticeably increased risk of malnutrition. 48% of CD patients in both the low and high disease activity groups had a reduction in muscle mass. Identification of the reduction in soft lean muscle mass in CD patients can be used as an indicator of disease activity.

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ĶERMEŅA MUSKUĻU MASAS METABOLO RĀDĪTĀJU ANALĪZE SAISTĪBĀ AR KRONA SLIMĪBAS AKTIVITĀTI

Krona slimība ir hroniska iekaisīga zarnu slimība ar slimības aktivitātes un remisijas periodiem. Iekaisīgas zarnu slimības ir kļuvušas par globālu problēmu. Krona slimības izplatība ievērojami pieaugusi pēdējo gadu laikā. Malnutricija ir bieži sastopama komplikācija Krona slimības pacientiem. Tā korelē ar slimības aktivitāti un izmaiņām ķermeņa kompozīcijā. Pārmaiņas ķermeņa kompozīcijā saistītas ar biežākām pēcoperācijas komplikācijām, ilgāku hospitalizāciju, samazinātu dzīves kvalitāti un augstākām veselības aprūpes izmaksām. Šī pētījuma mērķis bija analizēt ķermeņa muskuļu masas vielmāiņas rādītāju saistību ar Krona slimību un zemu vai augstu slimības aktivitāti. Pētījumā iekļauti 23 hospitalizēti Krona slimības pacienti vecumā ≥ 18 gadi. Pacienti tika novērtēti divas reizes, izmantojot malnutricijas skrīninga skalas *Nutritional Risk Score (NRS 2002)* un *Malnutrition Universal Screening Tool (MUST)*, kā arī tika veikta ķermeņa bioelektriskās impedances analīze. Pētījumā novērots, ka pacientiem ar augstu slimības aktivitāti bija ievērojami augstāks malnutricijas risks. Lielai daļai (48%) Krona slimības pacientu gan ar zemu, gan augstu slimības aktivitāti bija samazināta muskuļu masa. Muskuļu masas samazinājuma noteikšanu Krona slimības pacientiem var pielietot kā slimības aktivitātes rādītāju. Pētījumā konstatēts, ka ne tikai pacientiem ar samazinātu ķermeņa masas indeksu (ĶMI), bet arī pacientiem ar normālu vai paaugstinātu ĶMI ir augsts ķermeņa kompozīcijas izmaiņu risks.