

## The significance of nutritional strategies in patients with inflammatory bowel disease in the context of malnutrition and the development of malnourished obesity

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**Abstract:** Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, despite the increasing incidence, still do not have a specific etiology. Diet seems to be an important factor, modifying the occurrence of the disease and its course. Diet can affect the symptoms of IBD both directly, e.g., by alleviating diarrhea, bloating and constipation, and indirectly by shaping the microbiota. Bacterial metabolites produced under the influence of supplied nutrients may contribute to the modulation of pro- and anti-inflammatory pathways, depending on the diet used.

So far, IBD has been associated with weight loss and malnutrition. In recent years, a trend of sarcopenic obesity with concomitant malnutrition has been observed. The new phenomenon is called malnubesity. This work aims to review the most commonly used diets in IBD in order to evaluate them in terms of alleviating ailments, but also maintaining proper nutritional status and lack of obesity. Low-fiber, low FODMAPs, Mediterranean diet and Crohn's Disease Exclusion Diet diet were considered.

We assume that diet is modifiable factor that is related to nutritional status and healthy body weight. In addition, the current knowledge on the relationship between nutrition strategies, obesity and IBD will be demonstrated.

**Keywords:** Crohn's disease, ulcerative colitis, diet, malnutrition, malnubesity.

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## Introduction

Inflammatory bowel diseases (IBD) include main two forms: Crohn's disease (CD) and ulcerative colitis (UC). Despite the success of wide studies with CD and UC, the exact pathophysiology of these diseases remains largely unknown. It is linked to a complex interaction between the host's immune system and the gut microbiome. Given the increased prevalence of IBD, in countries that have adopted a western lifestyle, the prevailing theories suggest a significant contribution of the western diet to the development of IBD [1]. Current data indicate an increasing importance of environmental factors in the pathogenesis of CD [2]. In healthy individuals, the intestinal epithelium acts as a barrier to prevent foreign antigens, toxins, and microorganisms from entering the lumen of the epithelium. It consists of a mucous layer, epithelial cells and tight junctions between cells. The colonic mucus should be impermeable to bacteria [2]. Identification of environmental risk factors with plausible biologic link to disease risk is vital to improve our understanding of disease pathophysiology and course. The potential mechanism of this disease is complex and involves various factors, such as: immunological, genetic, lifestyle and changes in the intestinal bacterial microbiota. According to the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Crohn's and Colitis organization (ECCO), modifiable environmental factors preventing the occurrence of IBD include breastfeeding, physical activity, adequate sleep, high consumption of vegetables and fruits, a diet rich in omega-3 fatty acids and a proper level of fiber intake. Factors contributing to the occurrence of IBD include high consumption of saturated fatty acids, smoking and high exposure to stress [1].

To the most common clinical symptoms of UC belong: bloody diarrhea, abdominal pain, fever and weight loss. While anemia, malnutrition, palpable tumor over the right iliac crest and weakness are the most frequent symptoms of CD. Currently, over 3.5 million people worldwide suffer from IBD, but assumptions predict that the incidence will increase significantly in the coming years. The disease can affect people of all ages, often also young people, thus reducing their quality of life [3].

IBD progresses with exacerbations and periods of remission. The duration of remission is individual for each patient. Considering the research conducted so far, it seems reasonable that the course of the disease may also be conditioned by modifiable factors such as: diet, lifestyle, food and probiotic supplementation. The contribution of environmental factors is multidirectional. They influence directly on the intestinal mucosa, modulating the composition of the intestinal mucus, also contributing to the occurrence of IBD [4]. Environmental factors can influence the type of gut microbiota. The most important ones include dietary fiber intake, medications, antibiotics used, and the type of diet [4]. Despite many scientific reports regarding the

role of diet in the pathogenesis and treatment of IBD, there are still no consistent recommendations regarding the nutrition of patients.

Though, in IBD patients decreased body mass is expected, the association of IBD with obesity has been increasingly observed in recent times. Obesity is commonly measured by body mass index (BMI) and has been linked to increased levels of proinflammatory markers such as tumor necrosis factor alpha (TNF- $\alpha$ ) and C-reactive protein (CRP). According to the criteria of the World Health Organization, well-nourished patients are when BMI is 18.5–24.9 kg/m<sup>2</sup>, underweight or malnourished when BMI is <18.5 kg/m<sup>2</sup> and overweight when BMI is >25 kg/m<sup>2</sup>. Recent study showed that about 15–40% of adults with IBD are obese, whereas 20–40% are overweight [5]. Obesity at diagnosis was more common in patients with CD than UC, and increasing degrees of obesity were associated with an increased risk of IBD. Study showed that obesity is associated with a reduced rate of disease remission and increased risk of disease complication in CD. There was no effect for UC. Obesity promotes the development of colon cancer, as well as UC and CD [6]. Factors contributing to obesity in IBD include medications, mainly glucocorticosteroids and improper diet. At the same time, obesity itself is associated with intestinal dysbiosis, mucosal barrier dysfunction and activation of the pro-inflammatory response of adipocytes. Therefore, risk of disease complications might be increased in obese patients [6]. There is an increased risk of hospitalization and increase in inflammatory markers in both UC and CD, as well as a higher risk of developing colorectal cancer in UC patients [6].

Recently, the tendency of gaining body weight in IBD patients [5]. So far, the period of exacerbation of the diseases has been usually associated mainly with weight loss and malnutrition. Obesity does not always go hand in hand with a proper nutritional status. Obese patients may have latent deficits in lean body mass. Literature begins to describe the phenomenon of malnutrition in obesity, called “malnubesity”. Currently, many studies refer to the topic of excessive body weight as the cause of IBD, but only few studies concern the role of obesity during inflammatory diseases.

Mechanisms of malnutrition in IBD include malabsorption of nutrients, reduced food intake, enteric nutrient loss, increase of energy requirements and non-specific elimination diet used to reduce symptoms. Reported prevalence of malnutrition in IBD varies between 20–85% and several studies have reported weight loss in 70–80% of hospitalized IBD patients and 20–40% of outpatient [7]. CD patients are at higher risk of malnutrition due to the frequent location of the disease in the small intestine, where main processes of digestion and absorption of nutrients take place. Unlike UC, which is confined to the colon and has few direct effects of malabsorption [7]. The severity of malnutrition in IBD depends on the activity, duration and extent of the disease, and especially on the severity of the inflammatory response that drives catabolism and causes anorexia [8].

Patients with active IBD, especially poorly responded to medical treatment, are most at risk of malnutrition. Malnourished patients with IBD are at higher risk of exacerbation, frequent hospitalizations, severe infections, unscheduled surgery, longer hospital stay, postoperative complications and increased mortality [8].

The assessment of the nutritional status and the need of nutritional support play a crucial role in the clinical care of IBD [7].

### **Altered gut microbiota and their function in IBD**

Microorganisms, in particular bacteria, are modifiable factor related to the onset and course of the disease [9]. Microbiota is shaped from an early age by the type of delivery, breastfeeding, periods of expanding the diet, environmental factors, medications used (mainly antibiotics), psychosocial factors and diet [9]. Intestinal microbiota plays an important role in the process of digestion and obtaining energy from food. It is also responsible for the fermentation of undigested food residues. Moreover, a balanced gut microbiota is essential for the production of vitamins. It takes part in the increases the absorption on minerals. Microbiota also plays a key role in the immune process of the human body by modulating the work of the immune system and the inhibiting the growth of harmful bacteria, and has a trophic function, nourishing colonocytes. The gastrointestinal microbiota plays a key role in the metabolism of nutrients provided in the daily diet, especially dietary fiber. These changes involve mainly non-digestible carbohydrates, e.g., cellulose, hemicellulose, pectins and arabinose. The main product of bacterial transformations are short chain fatty acids (SCFAs), which are the basic source of energy for the intestinal epithelium-colonocytes [10]. They have a beneficial effect on the intestines, including anti-inflammatory properties and strengthen the integrity of the intestinal barrier, the function of which is disturbed in IBD [10]. SCFAs can play an important role in the intestine by directly affecting the activity and function of colonocytes.

Dysbiosis, a disorder in the composition and number of bacteria, can be caused by an improper diet, medical treatment, unhealthy lifestyle, amount of stress, smoking and alcohol consumption [11]. Dysbiosis can induce infiltration of inflammatory cells in the intestine that produce pro-inflammatory cytokines, exacerbating the inflammatory process, causing epithelial and intestinal damage and additional intestinal symptoms [11]. Most often, dysbiosis is described in the final section of the small intestine and in the colon, which are considered to be the clusters of intestinal bacteria. Additionally, the differences in the composition of the microbiota of people suffering from IBD, compared to healthy people, were described [4]. In general, in IBD patients the number of *Enterobacteriaceae* bacteria increases, thereby reducing the number of bacteria from the *Clostridium*, *Lactobacillus* and *Bacterioides* groups. The literature provides divergent SCFAs producing bacteria like *Faecalibacterium prausnitzii*, *Rose-*

*Burria hominis*, *Saccharomyces cerevisiae* and *Clostridium* cluster [12]. Patients with CD are characterized by a lower content of bacteria from the *Bacterioides* and *Lactobacillus* groups compared to healthy people [12]. All literature sources agree that the composition of the microbiota is modified by external factors and that the bacterial microbiota of our intestines affects the course of IBD. Western diet, characteristic of developed societies with high prevalence of IBD, is rich in saturated fats, sugar and processed foods, and at the same time low in fiber, fresh vegetables, antioxidants and vitamins, thus contributing to the development of dysbiosis and disturbances in the production of SCFAs. Studies have shown that the western diet is associated with dysbiosis, leading to disruption of SCFAs production and chronic inflammation. The western diet is considered one of the causes of IBD development, as well as is often linked to overweight and obesity [13]. The western diet has been shown to be associated with dysbiosis and is a significant environmental factor predisposing to the development of IBD in susceptible individuals. Recent meta-analysis showed that this dietary pattern is associated with an increased risk of developing both CD and UC. It also turns out that increased consumption of refined grains, red meat, high-fat dairy products and fast food was positively associated with the risk of developing CD and UC. Children who had western eating habits were more likely to develop CD. It has also been found that eating fast food before the disease increases the risk of developing UC [14].

Western diet is consisting also of ultra-processed food (UPF). Cohort study of over 116,000 participants showed that higher intake of UPF was associated with greater risk of IBD (HR 1.82, 95% CI 1.22–2.72 for 5 and more servings a day and HR 1.67, 95% CI 1.18–2.37 for 1–4 servings a day). Same time, regular diet, based on Mediterranean baseline were not associated with IBD incidents [15]. Additionally, this study observed that highest UPF intake was found in group of patients, for whom the western diet was typical [15].

Several studies have shown a reduction in disease activity and an increase in time to relapse after dietary practices associated with abandoning a western diet. However, the effectiveness of alternative diets in recovering from an IBD flare and maintaining remission has not been fully elucidated. Due to the description of the diet and its impact on IBD in many studies, it will not be described in detail [16].

In recent years, there has been increasing evidence of the relationship between obesity and microbiota [17]. Intestinal bacteria may lead to the development of obesity through increased energy absorption, the influence of metabolites on the hunger and satiety center, adipose tissue storage and inflammatory processes [17]. IBD patients are characterized by a reduced number of *Bacterioides*, while studies in obese people suggest a role of reduced them in development of obesity. The abundance of *Lactobacillus* also inversely correlates with obesity and the decreased level is observed in IBD [3, 17]. It is also known that dietary changes, including elimination diet with

a reduced amount of fiber, contribute to changes in the composition of the microbiota. Therefore, it seems important to conduct further research to check how nutritional modifications in IBD affect the microbiota and the potential increase in the prevalence of obesity in this population [3, 5].

## Diet in IBD

Nutrition is actually considered an integral method of treatment of gastrointestinal diseases. In the context of IBD clinical management, the role of the diet is probably underestimated. In general, the diet in IBD should not only prevent malnutrition, but also have an anti-inflammatory effect and promote the restoration of the proper microbiota. Diet represents one of the main determinants of human microbiota, therefore an improper, misbalanced diet can contribute to establish a condition of dysbiosis with multiple effects on the intestinal homeostasis.

Currently, there is no evidence in the literature describing malnubesity phenomenon, focusing rather separately on malnutrition and obesity and their complication in IBD.

According to the latest ESPEN guidelines, all IBD patients should have a nutritional consultation to adjust their diet [8]. In this article we reviewed the role of several diets and nutrients in the development and course of IBD. Despite the lack of precise dietary recommendations in patients with CD and UC, studies to date show the impact of specific diets on the intestinal inflammation. This paragraph will outline the link between different diets and the development and course of IBD. The relationship between eating strategies and body weight fluctuations, including the obesity, has not been described yet. We assume that diet is modifiable factor that is related to nutritional status and healthy body weight. In addition, the current knowledge on the relationship between nutrition strategies, obesity, and IBD will be demonstrated.

### *Low fiber diet*

The main strategy of dietary protocols in IBD patients is a low-fiber diet containing <20 g of fiber/day. However, the evidence for the efficacy of a low-residue diets in IBD is lacking. Nowadays, guidelines suggest the use of a low-residual diet only in patients with exacerbation and comorbid diarrhea, not all IBD patients in general [18]. ESPEN guideline suggests that there is no “IBD diet” that can be generally recommended to promote remission in IBD patients with active disease [18]. An Italian study evaluating 70 patients with non-stenosing CD, randomly assigned to follow a low-residue diet (~3 g/day of fiber) or a normal Italian diet (13 g/day of fiber) for a mean of 29 months, reported that there was no difference between the two groups in clinical outcome,

including symptoms, need for hospitalization surgery, new complications, nutritional status, or postoperative disease recurrence [19].

However, studies indicated that many types of fiber could have the positive effect on the gut microbiota, its diversity, and increased SCFAs production, and thus possibly on the maintenance of remission in IBD patients. A prospective longitudinal cohort study of patients with CD (n = 1130) and UC (n = 489) in remission examined the association between fiber exposure and the risk of disease flare. Moreover, CD patients with higher fiber intake were 40% less likely to experience a flare at six months than those with lower fiber consumption. Fiber is the primary substrate for SCFAs production. A diet low in fiber contributes to reducing the production of acids, thus reducing their beneficial effects like anti-inflammatory properties and supporting healing of the intestinal mucosa [20].

Taking all into consideration, fiber is a dietary component that increases butyrate synthesis, regulates intestinal peristalsis, and bacterial metabolites of fiber may contribute to the reduction of inflammation [2].

Thus, it seems that limiting dietary fiber intake should be temporary and used only in a select group of IBD patients such as severe activity of disease with diarrhea or strictures of the bowels. At the same time, it should be emphasized that there is ample evidence of the positive effects of dietary fiber in patients with IBD, hence most should not restrict it.

### *Low FODMAPs diet*

The low FODMAPs diet (LFD) restricts consumption of fermentable oligosaccharides, disaccharides, monosaccharides and polyols, which are short-chain carbohydrates (sugars). FODMAPs are osmotic short-chain carbohydrates that are not completely absorbed in the small intestine, absorb water and are fermented by the bacteria in the distal small and proximal large intestine. The result of this cycle is the production of gas, which could partially explain the excessive bloating and flatulence. Foods rich in FODMAPs include high-lactose dairy, excess fructose vegetables/fruits and food rich in fructans/galactans and polyols. Products such as dairy free from lactose, low fructans and galactans from vegetables and low fructose are allowed [21].

Many IBD patients experience episodes of irritable bowel syndrome (IBS), so the LFD diet can benefit them and help them achieve pain relief [22]. Alleviating the symptoms of IBS can improve the quality of life and reduce many of the discomforts that patients face [22].

Gershon *et al.* showed that an LFD may leads to an increased intestinal secretion and gastrointestinal motility and a shorter transit time resulting in reduced gastrointestinal symptoms in CD patients [23]. Other studies have attempted to verify if high-FODMAP diet (HFD) increases the intestinal inflammatory activity, barrier

dysfunctions, and visceral hypersensitivity. Moreover, study conducted on CD patients showed that LFD significantly reduced the intensity of abdominal pain, flatulence and the number of bowel movements. However, there was no effect on constipation [24].

Remission phase was also taken into consideration, both CD and UC patients were investigated into the effect of LFD and evaluating symptomatology, markers of inflammation and the intestinal microbiota. More than a half of patients with quiescent IBD reported reduced gastrointestinal symptoms after LFD compared to only 16% on the control diet. *Bifidobacterium adolescentis*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii* were present in a lower quantity in the LFD group than in the control diet group. Serum inflammation markers did not differ between the study groups, nor did the microbiome diversity [25].

The main goal of LFD is to change the composition of the microbiome towards restoring the desired composition. Thus, this diet may contribute to the improvement of the nutritional status of IBD patients and change their body composition. However, due to its eliminative nature, according to American College of Gastroenterology guidelines, it cannot be used for more than 8 weeks [26]. It is therefore necessary to identify a group of IBD patients who could measurably benefit from the introduction of this brief, temporary nutritional intervention.

### *Mediterranean diet*

The Mediterranean diet (MD) based on a high intake of fresh vegetables, fruits, whole grain products, cereals, nuts, legumes, polyunsaturated fat such as olive oil, intake of fish, a low-fat dairy product, red wine, as well as a low consumption of saturated fat, meat, and sweets. The Mediterranean diet also includes moderate amounts of dairy, especially fermented dairy products (such as yogurt, kefir, cheese) and eggs [27].

In Chicco's *et al.* study IBD patients used MD for period of 6 months [28] Diet intervention applied in 142 IBD patients to assess their nutritional status, quality of life, disease activity, and steatohepatitis. All study participants were given a dietary consultation, during which they received advice on how to change their current eating habits in order to eat according to the MD. There were observed significant improvements in quality of life and indicators of malnutrition in the participants. The number of patients with active inflammation decreased after 6 months on the diet from 24% to 7%, the number of patients with high C-reactive protein (CRP) levels was reduced from 50% to 37.5%, and the number of patients with fecal calprotectin levels greater than 250 mg/kg was reduced from 44% to 28%. In addition, it was noted that patients had improved anthropometric indices correlating with steatohepatitis and metabolic syndrome, which seems important in the context of development of mal-



nubesity [28]. There was a decrease in BMI to normal values, a decrease in the content of adipose tissue with simultaneous increase in muscle mass.

MD affects changing composition of microbiota, causing improvement of the ratio between pathogenic microorganisms such as *Firmicutes* and *Escherichia coli*, and beneficial bacteria including *Bifidobacterium spp.* and *Bacteroides fragilis* [29]. Moreover, an increase of proinflammatory organisms *Fusobacterium*, *Peptostreptococcus*, *Bacteroides vulgatus*, and *Bacteroides thetaiotaomicron*, and a decrease in probiotic bacteria, such as *Lachnospiraceae*, *Bifidobacterium animalis*, and *Streptococcus thermophilus*, may promote inflammation, DNA damage, and cancer cell proliferation, which contribute to the development of colorectal cancer, which risk is increased especially in UC patients [29].

Taking all into consideration, MD requires further intervention studies to assess its effect on IBD patients, but it seems to be a promising diet for those groups of patients.

### *Anti-inflammatory diet*

Anti-inflammatory diet (AID) consists of lean meats, fish, plain dairy, eggs, fruit, vegetables, legumes, wheat, coffee, tea and honey. Limited products are red meat, sugar, other dairy products, canned and processed food, alcohol, sweetened beverages.

Many organizations guidelines agree on the need to limit red meat consumption [30]. Meat is a source of protein, iron and vitamin B<sub>12</sub>, but red meat should be limited in favor of white, fish and legumes. Furthermore, meat contains saturated fat. Barnes *et al.* conducted study of 412 patients with UC treated with an aminosalicylate, reported that dietary intake saturated fatty acid was associated with increased risk of a flare. Moreover, red and processed meat contains a high level of organic sulphur and sulphate additives, which may increase the amount of sulphate for microbial produced hydrogen sulphide. End-products of protein fermentation, particularly H<sub>2</sub>S, ammonia and to a lesser extent, phenols have well-established detrimental effects on the colonic microenvironment and epithelial health [31]. In the cohort study, there was reported that high meat consumption, carnivorous dietary pattern, containing poultry, processed meat and red meat was associated with higher risk of UC development and this correlation was the strongest for red meat [32].

On the other hand, fish consumption is associated with polyunsaturated fatty acids (PUFA) delivery, which have demonstrated anti-inflammatory properties in chronic inflammatory diseases, including IBD. However, at the moment, there is no sufficient studies that would unequivocally indicate the effectiveness of using fish in IBD patients' diet [33].

Also, the consumption of dairy products can be controversial in IBD. Often, patients automatically exclude milk from their diet after IBD diagnosis, which is not reflected in the guidelines [18]. If a patient has a lactase deficiency and the

associated lactose intolerance, products with lactose should be excluded from the diet, replacing them with lactose-free. The use of dairy products in the diet helps to control the calcium metabolism, which may be disturbed in cases of malabsorption and with steroid treatment [34].

Fruit contains phenolic acids, which has an anti-oxidative and anti-inflammatory properties. Daily consumption of fruit decreased the odds for CD (OR 0.39; 95% CI: 0.22–0.70) and UC (OR 0.56; 95% CI: 0.33–0.95). Vegetables are important source of dietary fiber and antioxidants, including vitamins A, C and E, minerals, trace elements and phenolic compounds. The anti-inflammatory properties of these phenolic compounds can be used as a natural source for the prevention of IBD. Research shows that patients consuming more vegetables were less likely to have CD (OR 0.85 95% CI: 0.74–0.97) [35].

### *Crohn's disease exclusion diet*

Of the various diets tested so far, the Crohn's Disease Exclusion Diet (CDED) is currently the best documented dietary management for the treatment of the active form of CD in children. The Crohn's Disease Exclusion Diet combines a specific elimination diet with partial enteral nutrition (PEN). PEN is a feeding strategy based on the administration of a liquid enteral formula that does not cover 100% of total energy requirements along with whole foods [36]. Exclusive enteral nutrition has been successfully used in the group of pediatric patients for many years. For this reason, for several years, attempts have been made to apply this strategy also in adults. Currently, there are no studies on larger groups of adult patients, but preliminary research seem to be promising [36].

The CDED diet is based on the exclusion of certain ingredients that abound in the western diet, which can weaken intestinal barrier function, generate dysbiosis or disrupt bacterial clearance mechanisms. In order to restore patients, lean body mass, the diet includes large amounts of high-quality protein and foods rich in complex carbohydrates. Three categories of food can be distinguished: mandatory, permitted and prohibited. As a result, patients take in adequate amounts of useful fiber and substrates necessary for SCFAs production. The CDED diet consists of three phases that change every six weeks, becoming increasingly simple for patients. The first phase is the strictest, because in addition to eliminating foods and dietary components that cause inflammation, certain fruits and vegetables are restricted to avoid excessive intake of dietary fiber. PEN is added to cover 50% of daily energy requirements. The second phase, which lasts another six weeks, allows for a greater variety of foods. Potentially harmful ingredients and foods that were previously not allowed, such as gluten, fatty fish, red meat and legumes, are introduced in a controlled manner to provide greater dietary flexibility and improve quality of life. Increased fiber intake is

also allowed, so that almost all fruits and vegetables can be included in the final weeks of this phase. PEN is reduced to an amount that realizes 25% of daily energy requirements. After 12 weeks of treatment with the diet, a maintenance phase begins, in which any meals are allowed on 1–2 days a week. This allows the diet to be balanced in such a way that the final phase does not have a specific duration, but rather becomes a long-term, sustainable, healthy lifestyle. It is recommended that PEN be continued, realizing 25% of daily energy requirements [36].

A CDED diet combined with enteral nutrition was shown to be more successful in inducing remission and to be better tolerated than enteral nutrition alone in a 12-week intervention involving 74 patients (mean age  $14.2 \pm 2.7$  years). The children received 50% of their caloric needs from an oral diet and 50% from enteral nutrition (Modulen formula) for the first six weeks, but for the following seven to twelve weeks, just 25% of their needs were met by the industrial diet. In both groups (CDED) and exclusive enteral nutrition (EEN), CRP decreased: in EEN, from 24 mg/dL to 4.1 mg/dL; and in CDED, from 23.6 mg/dL to 5 mg/dL. The composition of the gut microbiota is impacted by both EEN and PEN. Both diets had a similar impact on microbial activity during the first six weeks, with increased commensal *Clostridia* and decreased *Actinobacteria* and *Proteobacteria* abundance. The microbial composition between weeks 6 and 12 in CDED + PEN remained similar, however, the changes were reversed in EEN [37].

The CDED diet is as effective as total enteral nutrition in achieving clinical and biochemical remission but is superior to EEN in terms of patient tolerance. The elimination diet in Crohn's disease, unlike EEN, is a long-term strategy for maintaining remission and is nutritionally balanced. By including dietary fiber, it corrects the intestinal dysbiosis present in these patients, and is therefore a much more multi-directional and advanced approach than EEN, if followed properly. Due to the elimination nature of CDED, it should be administered under the supervision of an experienced clinical dietitian, who will ensure that the diet is properly balanced to reduce the risk of nutritional deficiencies and malnutrition in the patient. The CDED diet is a long-term strategy that can be used as monotherapy or combination therapy, gradually reducing drug treatment [38].

## Obesity

It has been proven that the obesity negatively affects disease course and treatment response in several immune diseases, but there is limited synthesis of data on the effect of obesity in IBD. Obesity and its related comorbidities have been observed in growing number of IBD patients, which previously was believed to be a condition characterized by undernourishment and low BMI. Increasing evidence show that IBD does not strictly imply hyponutrition but frequently leads to malnutrition, with an increased risk for IBD patients to be overweight or obese [5].

A British cohort of over 600,000 participants showed an association between obesity and an increased risk of CD, but no association was found for UC (HR 1.34, 95% CI 1.05–1.71) [13]. Moreover, each 5 kg/m<sup>2</sup> increase in BMI significantly increased risk of CD [13].

Interestingly, in the Danish National Birth cohort, the association between pre-morbid BMI and risk of CD was U-shaped, as women with a BMI <18.5 were also at increased risk of developing CD compared with women of a normal BMI (HR 2.57, 95% CI 1.30–5.06) [39]. Lomer *et al.* studied 390 IBD patients from Greece and United Kingdom found a prevalence of overweight and obesity of 29% and 18% respectively with only 16 patients (4%) underweight [40]. Moreover, excessive visceral adipose tissue (VAT) has been associated with complicated disease, higher rate of postoperative recurrence in CD, severe disease course, thus implying that adipose tissue might worsen inflammation in IBD [5]. Finally, obesity has been associated with poor response to conventional and biological therapies in both CD and UC [5].

Swiss cohort study (n = 3075) showed that 10% of subjects were obese and obesity was associated with a more severe exacerbation of CD. In addition, obese patients were less likely to achieve clinical remission and had higher level of calprotectin. However, no such relationship was observed for UC [41].

Interestingly, use of bariatric surgery, commonly used method to treat obesity, and the accompanying weight loss may reduce the risk of developing IBD. Significant differences were observed for sleeve gastrectomy (OR 0.63; 95% CI, 0.53–0.75) and gastric banding (OR 0.60, 95% CI, 0.46–0.80) but not for Roux-en-Y gastrojejunostomy (OR 0.83; 95% CI, 0.68–1.03) [42].

Obesity leads to adipose hypertrophy and dysfunction. It may come to secretion of many proinflammatory mediators that are elevated in CD and is linked to alteration in gut microbiome [13].

Moreover, being overweight or obese might lead to gut inflammation in IBD. Lymphocytes and macrophages in adipose tissue produce several pro-inflammatory cytokines IL-6 and TNF- $\alpha$ , that might promote inflammatory responses in the gut of obese patients. It has also been observed that an increase in zonulin, a marker of increased intestinal permeability, is associated with excess adiposity. The excess of adipose tissue contributes to increased synthesis of proinflammatory interleukins such as IL-6, IL-17 and TNF- $\alpha$  [43]. Patients with IBD show a unique form of VAT, called creeping fat, whereby mesenteric fat hyperplasia is limited to areas of inflamed bowel [44]. This creeping fat in CD patients tend to be more immunologically active than other VAT, and its extent correlates with histological inflammation. Moreover, the expression of leptin and adiponectin has increased in the hypertrophied mesenteric fat of patients with CD. Levels of other adipokines, such as resistin, also correlate with CD severity and disease activity [44].

## Malnubesity

Malnutrition might occur both UC and in CD. The main determinants of malnutrition in IBD are decrease of oral food intake, higher level of inflammatory cytokines, gastrointestinal nutrient loss and biliary salt diarrhea. Patients with active IBD often experience loss of appetite due to nausea, vomiting, abdominal pain, and diarrhea. They also report anxiety about possible exacerbation of their complaints after eating. Medications may also induce nausea, vomiting, or anorexia [45]. Moreover, glucocorticoids often reduce absorption of phosphorus, zinc and calcium and may lead to osteoporosis [7]. Long-term therapy with sulfasalazine may be associated with anemia due to being a folic acid antagonist [7].

Disease affecting the small bowel leads to a greater incidence of protein–energy malnutrition and specific nutrient malnutrition than colon disease. The prevalence of protein–energy and specific nutrient malnutrition seems to be higher in CD compared to UC, probably because it can affect any part of the gastrointestinal tract and, mainly, the small bowel, responsible for digestion and absorption [46]. In addition, patients with CD generally develop malnutrition over a long period of time, whereas patients with UC tend to be relatively well nourished whilst in remission they can develop precipitous nutritional deficiency during a hospital admission for a severe acute relapse [21, 46]. Significant aspect of malnutrition in IBD is linked with fluctuations in body composition, in particular of the ratio between fat mass (FM), including VAT and subcutaneous adipose tissues, and lean mass, called fat-free mass (FFM) [47]. In malnutrition it is not only about low body weight, measured by BMI. Many times, due to normal or even excessive BMI, there is a decrease in lean body mass (LBM) and thus malnutrition. The altered body composition in IBD patients may impact on the course of the disease, responsiveness to treatment methods, outcomes of surgery and quality of life [48]. Biliary salt diarrhea is commonly associated with terminal ileal disease with impaired absorption of lipids and fat-soluble vitamins. The malabsorption of fat may lead to steatorrhea.

Systematic review found that up to 60% of IBD patients have reduced muscle mass compared to healthy individuals [49]. Other study has shown that many of sarcopenic IBD patients — 41.5% had a normal BMI, therefore could have been classified as well nourished by traditional measurements. In addition, 20% of sarcopenic patients were overweight or obese [50]. Sarcopenia was associated with increased need for surgery and poor surgical outcomes in IBD [50].

It also seems important to choose the right tool for assessing nutritional status. Serum albumin levels, the most frequently tested to identify the nutritional status, might not be a sufficient indicator, especially in the active phase of the disease, because of the negative effect of inflammatory cytokines on this plasma protein.

## Conclusions

Nutritional factors in IBD are significant as they potentially influence disease activity, course and morbidity. Individual dietary components can modify the course of intestinal inflammation, both promoting exacerbation and quieting it. Moreover, they can influence the restoration of the balanced gut microbiome. However, there is still no known nutritional pattern to offer for IBD patients. It seems that the type of diet used should depend on the activity of the disease rather than the type of IBD. Moreover, current studies show that a poor nutritional status, as well as selective malnutrition, sarcopenia or new phenomenon malnubesity is associated with poor clinical outcomes, response to therapy, and, therefore, quality of life. The phenomenon of malnubesity may seem confusing to clinicians because body weight appears to be normal. In such a situation, it is easier to overlook inadequate nutritional status and not react properly.

Given the increasing number of IBD patients with excessive body weight and associated malnutrition, BMI assessment is not a useful tool for detecting malnutrition. Therefore, the periodic nutritional assessment should include a dietetic evaluation with the comprehensive assessment of daily caloric intake, eating pattern, energy expenditure, and analysis of body composition. Not only during exacerbation, but also periodic nutritional assessment should be applied in remission. Considering the multifactorial impact of external factors on the nutritional status and body weight, it seems important to clarify the guidelines on nutrition and emphasize the role of a dietitian in patient care.

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