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Review

Hot Topics on Nutrition in IBD

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Abstract

Inflammatory bowel diseases (IBD) affect primarily the bowel, but they are multisystemic diseases with a wide range of extraintestinal manifestations and complications. Nutritional imbalance occurs frequently in patients with IBD. The spectrum of malnutrition goes from undernutrition (low protein-caloric intake, disease-related malnutrition, micronutrient deficiencies) to overnutrition and obesity. The nutritional status of patients with IBD is increasingly recognized as a key aspect of the treatment and must be addressed in all patients. The screening and correction of the deficiencies should be individualized. Except for enteral nutrition in pediatric Crohn's disease, no clinical evidence supports specific diets. Nevertheless, the role of personalized nutritional interventions as an adjunct therapy is well established. Compelling new data points to a key role of diet in gut inflammation directly or through modulation of intestinal microbiota. It will be of utmost importance to have well-designed longitudinal studies on dietary interventions alone or combined with current therapies. This review summarizes topics such as the spectrum of malnutrition, the evidence behind the concept of diet as an IBD cause, and the role of diet in IBD therapy.

Keywords

IBD; nutrition

1. Background

Inflammatory bowel disease (IBD), mainly represented by ulcerative colitis (UC) and Crohn's disease (CD), is characterized by chronic relapsing and remitting inflammation of the gastrointestinal tract [1]. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations [1].

In recent years, the epidemiologic evolution of IBD has brought some clues to the real-life impact of the environment, especially diet, on IBD etiology and progression [2]. The rising incidence and prevalence of IBD globally coincide with the adoption of Westernized lifestyles, particularly dietary habits [2]. In fact, with the advent of globalization and newly industrialized countries' transition from "developing" to "developed," dramatic rises in the incidence of IBD in Asia, Latin America, South America, and Africa occurred [3, 4].

Patients with IBD have a higher risk for nutritional deficiencies, especially in the active phase, but also when the disease is in clinical remission [5]. In contrast, there is also an increased prevalence of patients who present overnutrition during follow-up [6, 7]. Therefore, nutritional status should be routinely accessed during diagnosis and disease course [1]. Beyond that, a standardized nutritional care process with a systematic pre-defined sequence of steps implemented by a multidisciplinary team should be an essential part of IBD treatment [8-10].

1.1 A Delicate Balance: From Under to Overnutrition

Malnutrition encompasses both undernutrition and overnutrition, defined as a condition arising from insufficient food intake or nutrition, leading to changes in body composition and body cell mass, ultimately resulting in diminished physical and cognitive function and potentially adverse clinical outcomes [9].

According to WHO, in the strictest sense of the term, malnutrition englobes undernutrition (which manifests in four forms: wasting, stunting, underweight, and micronutrient deficiencies), micronutrient-related malnutrition, overweight, obesity, and diet-related noncommunicable diseases, such as heart disease, stroke, diabetes and some cancers (Table 1) [8, 11, 12].

Table 1 Diagnostic criteria for undernutrition, obesity, and overweight.

Diagnostic criteria
Undernutrition, according to GLIM criteria, included three phenotypic criteria (non-volitional weight loss, low body mass index, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation and inflammation or disease burden). To diagnose undernutrition, at least one phenotypic criterion and one etiologic criterion should be present [8].
Obesity is defined as a BMI of 30 kg/m² or higher and **overweight** as 25-29 kg/m² [12].

Malnutrition is a bad prognostic factor as it is associated with multiple adverse events: a higher number of emergency admissions, more hospitalizations and a longer inward period, urgent surgeries and, therefore, postoperative complications, lower quality of life, and even higher global

mortality [13, 14]. In addition, malnutrition can trigger inflammation through a complex crosstalk that might lead to a malnutrition-inflammation vicious cycle [15].

The ESPEN guideline recommends malnutrition screening for all patients with IBD at diagnosis and subsequent reassessment [16]. Nevertheless, no explicit recommendations are provided regarding the optimal screening and assessment process, nor is a clear discussion on the most accurate tools to be utilized presented. Despite the advancements in the development of screening tools to assess nutritional risk, more advanced research is required to understand the application of these tools in IBD populations [15, 17]. Considering this, the Universal Screening Tool for Malnutrition and the Nutritional Risk Screening-2002 tool are recommended for patients with IBD [18-23]. A comprehensive nutritional assessment should be promptly conducted upon detection of malnutrition or the risk of malnutrition during screening. A proposed evaluation approach to the nutritional status of patients with IBD is presented in Figure 1.

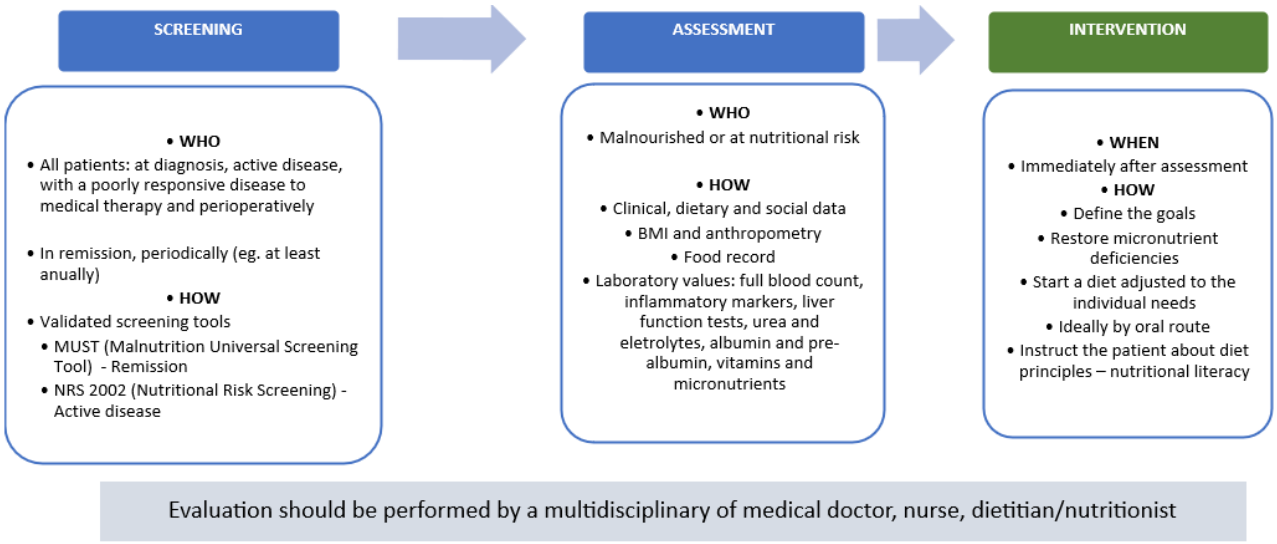

Figure 1 Proposed evaluation approach of nutritional status of IBD patients.

1.1.1 Undernutrition

According to the literature, the prevalence of undernutrition in IBD ranges between 10% and 35%, with some studies reporting values as high as 70% [24-28]. This altered nutritional status can occur either with active disease or at remission and affects both UC and CD patients, even though it is more common in the latter [27]. Regardless of the IBD subtype, the 2 major risk factors for undernutrition are the severity of disease activity and the extension of gastrointestinal involvement [24]. The underlying mechanisms include reduced oral food intake, malabsorption, enteric losses, increased energy requirements, and iatrogenic factors. The reduced food intake may be due to loss of appetite associated with gastrointestinal symptoms, such as abdominal pain, nausea, or vomiting, either associated with the disease or as an adverse effect of several medications [29]. Loss of epithelial integrity and impaired mucosal transport of ions and nutrients leads to malabsorption and enteric losses of electrolytes and fluids [30-32]. Blood and proteins are also lost through the intestinal lumen due to mucosal inflammation. Furthermore, bowel resection is also associated with impaired absorption and can induce watery or bile salt diarrhea and steatorrhea [33-36]. As a consequence of surgical removal of the ileocecal valve and in association with chronic inflammation,

small intestinal bacterial overgrowth is common in IBD, another risk factor for maldigestion and malabsorption [37-39].

Thus, patients with IBD have a higher risk of protein-energy malnutrition, altered body composition, and micronutrient and vitamin deficit [40].

1.1.2 Overweight and Obesity

On the other side of the spectrum, and even though in the past, obesity has not been associated with IBD, recent epidemiologic changes are revealing an increase in the number of patients with obesity and pointing to obesity as a risk factor for IBD. The globalization of the Western lifestyle accompanies the dramatic increase in obesity prevalence, which has nearly tripled since 1975 [41]. IBD numbers follow the same trend, probably due to sharing risk factors such as an unhealthy diet and a sedentary lifestyle [4]. Furthermore, obesity may act as a risk factor for IBD. Even though studies are ambiguous, there is some evidence that higher weight in adolescence is associated with an increased risk of Crohn's disease but not ulcerative colitis [42-44]. According to the literature, 15-40% of adults with IBD are obese, and an additional 20-40% are overweight [45-49]. Furthermore, this relationship seems to be bidirectional, as recent studies conclude that IBD patients might have a significantly higher risk of obesity. Suggested explanations involve dysbiosis, altered metabolic intestinal signaling mediated by hormones, satiety-related peptides dysregulation, and lateral effects of therapy mainly due to corticosteroids but also biological therapy [50-52].

1.2 Beyond Malnutrition: Recognizing Sarcopenia

Sarcopenia is a multifactorial progressive generalized syndrome characterized by decreased skeletal muscle mass, strength, and muscle function [53]. It results from malnutrition and disease-related wasting, decreased physical activity, and aging [15].

Myopenia and pre-sarcopenia are present in more than one-third of patients with IBD, and nearly 20% are sarcopenic [54, 55].

This is a concerning fact because there is an association between myopia and poor outcomes, such as an increased risk of IBD therapy failure, postoperative complications, and low bone mineral density [54].

Notably, sarcopenia is independent of body mass index (BMI). In a retrospective study involving 90 IBD patients, 41.5% were normal weight, 14.6% were overweight, and 4.9% with obesity were sarcopenic [56].

This highlights the need for sarcopenia screening in all patients with IBD and not just those who appear malnourished to avoid underdiagnosing [12].

2. From Cause to Therapy?

2.1 Diet as an Ethological Factor

Diet is thought to play a pivotal role in intestinal inflammation due to the complex interplay between a patient's diet and its regulatory effects on the microbiota, the gut immune system, and epithelial barrier function [57-60]. In the past decade, there has been an increasing elucidation of the mechanistic basis of experimental diet-induced gut inflammation. Moreover, translational and clinical evidence suggests that IBD arises from perturbation of diet-microbial-immune system

interaction [61]. Diet can influence the IBD course through several direct and indirect mechanisms. Firstly, dietary components can affect epithelial barrier integrity by altering structure and permeability through modulation of tight junctions and disruption of colonic mucin. Furthermore, dietary ligands may directly affect immune cells [62-65]. Secondly, diet influences microbiota (bacteria, viruses, and fungi) with downstream effects on immune activity [61, 66]. Evidence indicates that dysbiosis promotes susceptibility to gut inflammation, and dietary changes cause alterations in the gut microbiota composition [67, 68].

Recent evidence suggests that specific nutrients and additives instigate gut inflammation. The Western diet promotes intestinal inflammation in genetically susceptible individuals by increasing the intake of calories derived from polyunsaturated fatty acids, digestible carbohydrates, animal protein, and food additives [57, 69, 70].

2.2 Diet as Therapy

2.2.1 Recent Advances

Current treatment strategies rely on immunosuppressive, immunomodulatory, and biologic therapies, which are expensive and associated with potentially serious side effects [71]. In addition, a therapeutic ceiling seems to exist as many patients do not achieve remission despite there being more therapeutic options than ever before [72, 73]. Most biologics have only achieved a clinical remission rate of approximately 40% at 52 weeks [74]. Several strategies have been proposed to surpass the therapeutic ceiling in the future, including the combination of biologics/small molecules, the integration of drugs and nutrition, and the modulation of gut microbiota [75]. Using diet as an adjuvant therapy is an attractive strategy relying on accessibility and lack of associated complications [71].

There is an increasing interest in understanding the role that diet may play in the pathogenesis and management of patients with IBD. Considering the metabolic underpinning of IBD, diet reflects a critical rheostat of gut inflammation in IBD [61].

First, the risk of malnutrition should be evaluated by a dietitian with validated screening tools [17, 20]. Micronutrient deficiencies should be regularly checked, even in the remission phase. Specific deficits should be carefully identified and properly corrected [76].

Nowadays, diet is considered a major therapeutic tool for patients with IBD. Growing evidence corroborates its efficacy as a non-pharmacological management strategy in IBD. Next, we summarize the most consensual dietary guidance in IBD, either in the active or remission phase, as the therapeutic objectives are specific (Figure 2 and Figure 3, respectively).

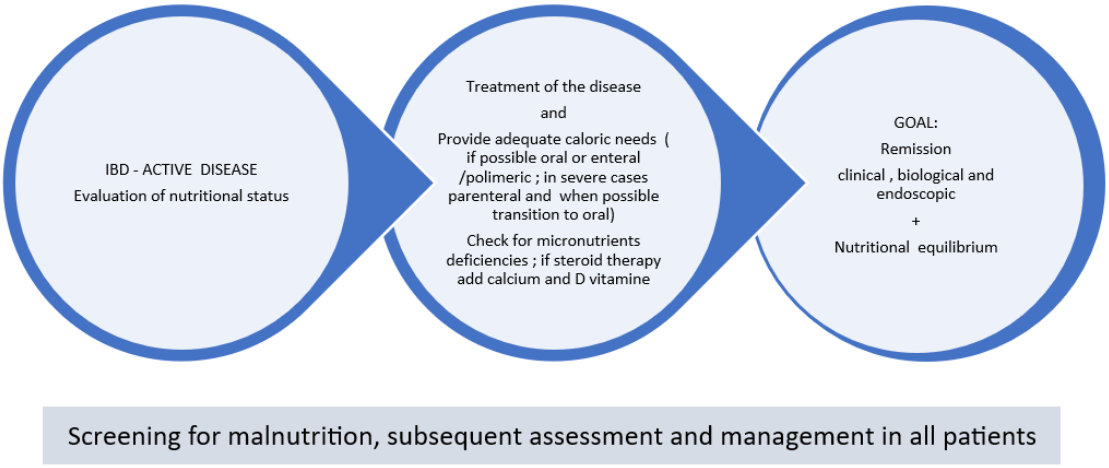

Figure 2 Nutritional intervention objectives in active IBD.

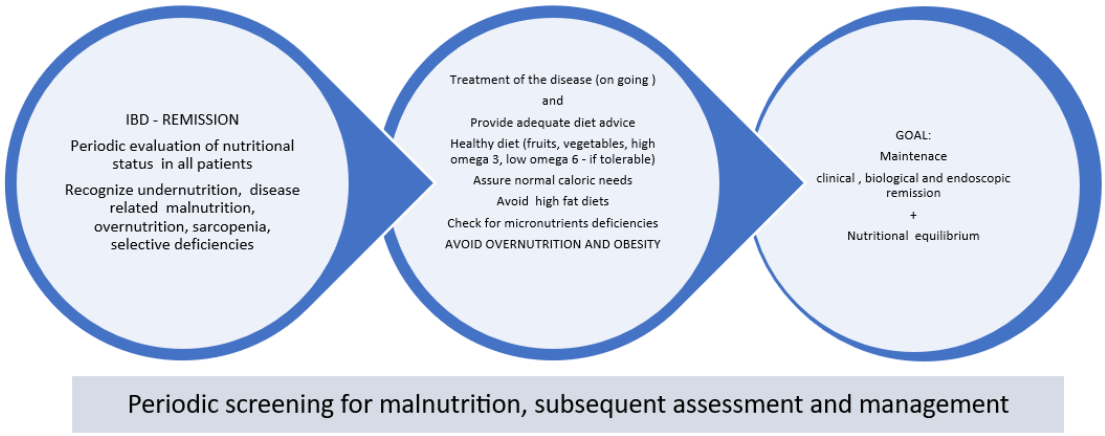

Figure 3 Nutritional intervention objectives in remission.

Special cases, such as patients at perioperative evaluation, are not included in our narrative review.

2.2.2 Active Phase

Exclusive Enteral Nutrition. In pediatric CD patients with mild to moderate disease activity, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Crohn's Colitis Organization (ECCO), and European Society for Clinical Nutrition and Metabolism (ESPEN) recommends exclusive enteral nutrition (EEN) as first-line treatment for induction of remission both in the first flare-up and during relapses of symptoms [76-80]. It uses a nutritionally balanced polymeric formula as the unique source of daily energy requirement for 6-8 weeks [81]. Many studies, including systematic reviews, meta-analyses, and Cochrane reviews, proved EEN to be as effective as steroid therapy in inducing clinical, mucosal, and transmural remission [82-87].

Regarding adult patients, even though data is heterogeneous and lacks power, some studies suggest that EEN alone might have a similar remission rate as corticosteroids and, in addition to infliximab, may improve induction and persistence of remission [88]. Thus, EEN can be considered for remission induction in some adult patients with CD. Concerning UC, even though it may improve symptoms and nutritional status, there is no current data to support EEN routine use [89].

The mechanism of action of EEN is not yet fully understood, but it is hypothesized that the basis of its therapeutic achievement works through a modulation of gut microbiota [90-92]. A major drawback of this therapy, especially in adults and in the long term, is its restrictive nature, palatable monotony, and, thus, poor compliance. Furthermore, gut inflammation increases when patients resume their diet [92].

In order to overcome this, in the past years, new dietary strategies have been developed to achieve similar results as with EEN and to be more tolerable.

Crohn's Disease Exclusion Diet. Knowing that partial enteral nutrition (PEN) in association with an unrestricted diet is ineffective in inducing clinical remission, Crohn's Disease Exclusion Diet (CDED) was conceived [93, 94]. CDED is a whole-food diet with restrictions on certain foods and dietary components associated with a negative gut impact [95]. This specific exclusion diet combines varying amounts of PEN over time, including an induction and maintenance phase. In a study with 47 CD patients (34 children and 13 young adults) without any medication for inducing remission, treatment with polymeric formula covering 50% of daily energy requirements plus selected foods for the remaining needs showed a 70% clinical remission, evaluated with the Harvey-Bradshaw Index (HBI) and PCDAI, after 6 weeks. For 14 patients, this was the initial treatment approach, while for all others, the treatment was initiated following a lack of response or relapse to a previous therapy. The formula was subsequently reduced to 25%, accompanied by a gradual introduction of selected foods, resulting in 84% of patients remaining in remission [95]. A significant reduction in inflammatory markers was also observed. Although promising, it is imperative to critically analyze the results, given that the studied population primarily consisted of patients with a relatively short duration of uncomplicated disease, and the analyses were conducted retrospectively.

Furthermore, a multinational, randomized head-to-head controlled trial compared CDED + 50% PEN during 6 weeks followed by CDED + 25% PEN during weeks 7 to 12 versus EEN for 6 weeks followed by free diet + 25% PEN. 78 pediatric patients with luminal mild to moderate active CD without medical therapy were included. CDED seems as effective as EEN in inducing clinical remission and superior in achieving sustained remission rates [96]. It is important to notice that the study's primary endpoint was tolerability at week 6 and that clinical remission without steroids was a secondary endpoint. This trial was an induction study without data on endoscopic response or remission. Both diets successfully induced remission by week 6; CDED + PEN was better tolerated than EEN. The authors also examined microbiological data and demonstrated that the microbiome's composition changed in response to the implemented diet, aligning with the observed changes in inflammatory parameters.

Regarding the adult population, data is still scarce [97]. A recent randomized trial involving 44 biologic naive adults aged 18-55 years with mild-to-moderate Crohn's disease demonstrated that CDED with or without PEN was effective for induction and maintenance of remission and might lead to endoscopic remission [98]. The main limitations were the low sample size and the duration of follow-up (24 weeks), but the concept is up-and-coming. It is essential to conduct additional studies, particularly those involving endoscopic assessment, to replicate and validate these findings.

ESPEN current guidelines state that CDED + PEN should be considered an alternative to EEN in pediatric patients with mild to moderate CD to achieve remission [grade of recommendation B; Strong consensus 100% agreement]. A CD exclusion diet can be considered with or without EN in adult patients in mild to moderate active CD [grade of recommendation 0; strong consensus 95%

agreement] [76]. It is important to note that data on long-term effectiveness and possible risk of nutritional deficiencies or eating behavior disturbances are not yet available.

Other Diets. Several studies on using other diets in IBD to induce remission have been published in the literature. Due to the lack of robust RCT on these dietary approaches, the following diets are still not recommended by guidelines.

Crohn's Disease Treatment with Eating Diet. Crohn's Disease Treatment with Eating Diet (CD-TREAT) is a restrictive diet where lean meats, fish, eggs, some fruits, and vegetables are allowed while excluding lactose, gluten, processed meat, and some additives. The objective of this diet is to match the composition of EEN through the use of ordinary whole foods. A clinical trial evaluating the effect of CD-TREAT in healthy adults, rat models, and children with CD demonstrated that CD-TREAT can replicate EEN changes on the gut microbiome and decrease gut inflammation. Among 5 children with mild to moderate active CD, 4 (80%) had a clinical response after 8 weeks on CD-TREAT, and 3 (60%) entered remission, with significant concurrent decreases in fecal calprotectin [99]. It is important to notice that 3 patients were on thiopurine and 1 on combination therapy with thiopurine and anti-TNF. These findings are limited by the small sample size and the absence of both a comparator and randomization.

The Specific Carbohydrate. The Specific Carbohydrate Diet (SCD), initially designed by pediatrician Dr. Sydney Haas for treating celiac disease patients, has demonstrated good results for IBD patients. It excludes all grains, refined sugars, processed foods, and dairy aside from yogurt fermented >24 hours and some hard cheeses. In a study evaluating 417 pediatric and adult IBD patients on SCD, with or without medical therapy, 36% reported clinical remission by one to three months, and 47% reported improvement in laboratory values [100]. Clinical remission was evaluated with a self-applied online questionnaire, which has not been validated as a tool to assess IBD, thus limiting the results of this study. A small retrospective study including seven children with CD showed clinical and biological remission in all patients in 3 months [101]. Additionally, a prospective study with SCD therapy solely, in pediatric patients with active CD, evaluating small bowel mucosal healing on capsule endoscopy by 12 weeks, demonstrated that 4 of the 10 patients (40%) achieved mucosal healing (Lewis Score < 135), with 8 of 10 showing significant mucosal improvement when compared with baseline [102]. Furthermore, SCD also showed positive results for UC pediatric patients, although data is limited by small sample sizes and methodological heterogeneity, with concomitant immunomodulatory/biological therapy as a potential confounder [103, 104].

The Mediterranean Diet. The Mediterranean diet (MD) is characterized by a high consumption of vegetables, fruits, cereals, nuts, legumes, and unsaturated fat, a moderate intake of fish and dairy, and a low consumption of saturated fat, meat, and sweets.

In a randomized trial with 191 adult patients with CD, comparing SCD with MD, SCD was not superior to achieving symptomatic or biological remission. Thus, due to the greater simplicity of MD and other already proven health benefits, it is suggested that MD may be preferred to SCD for most patients with mild to moderate CD [105]. An important feature of this study was high self-reported adherence in the first 6 weeks while prepared food was provided to the patients. After that, patients were responsible for buying and preparing their meals, and a decline in self-reported adherence

was noticed. This reflects the challenge of maintaining a long-term dietary plan. Another prospective study involving 142 adult patients (84/58 UC/CD) with mild disease and six months of follow-up showed improved CDAI and Mayo scores and decreased CRP and fecal calprotectin [106]. The selected population might influence the result, which mainly consists of patients already in remission.

Ulcerative Colitis Exclusion Diet. Ulcerative Colitis Exclusion Diet (UCED) was evaluated in a randomized control trial with adult patients refractory to medical therapy, in addition to fecal microbiota transplantation (FT) or alone. A safety monitoring board stopped the study for futility as UCED alone achieved higher clinical remission and mucosal healing than single donor FT with or without diet [107].

2.2.3 Remission Phase

According to ESPEN guidelines [76], there is no specific diet recommendation for IBD patients in the remission phase. None of the alternative diets seem effective in obtaining and maintaining remission. Thus, patients should follow a general healthy diet, and dietary plans should be individualized.

As an example, patients with IBD and irritable bowel syndrome (IBS) symptoms may benefit from low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet. FODMAPs consist of non-digestible components in foods fermented by colon bacteria and may elicit IBS symptoms. There is no evidence of the efficacy of a low FODMAP diet in reducing inflammation and induction/maintaining remission. This diet may be considered in patients with IBD and IBS symptoms in order to improve functional symptoms [81, 108].

Patients with known intolerances also benefit from dietary adjustments: reducing high-lactose-containing products and/or using lactase-treated products if lactase deficiency is suspected [81].

Thus, diets should be customized during dietary counseling to avoid the patients' food intolerances, and restrictions should be carefully advised to diminish the risk of malnourishment [76].

3. Unmet Needs - The Main Questions for Research

There are still crucial clinical questions that need further clarification: how to appropriately screen for nutritional status and identify IBD patients at nutritional risk; by what methods can clinicians systematically and effectively implement nutritional care algorithms on a day-to-day basis; by what means can clinicians and nutritionists articulate and complement each other within a protocol-based framework; how to personalize our patient's diet at a specific time and circumstance and how long should a diet plan be implemented, either for induction and for remission phases. Even though there is increasing evidence of the importance of nutritional care in patients with IBD, little is known about how IBD centers are implementing these strategies. Standardized protocols should be developed and structurally implemented in everyday clinical practice [10].

As further research is needed, the question of how to ensure quality in clinical nutrition research remains. The recent and emerging field of nutrition precision enables the design of personalized dietary interventions to impact the management of different diseases [109]. It aims to provide high-definition nutrition recommendations based on integrating multiple factors such as genetics,

microbiome, metabolic profile, health status, physical activity, dietary pattern, food environment, and socioeconomic and psychosocial characteristics [110].

Recognizing that a healthy diet for one individual may not be for another and that health status and dietary therapy efficacy are dynamic, nutrition precision may be a framework to predict individual patient responses to food [109].

Integrating personalized dietary strategies in the management of our IBD patients seems to be the right path to improving quality of life by inducing remission and preventing relapse.

Nutrition research has many challenges, and clinicians lack data from high-quality research and predictive tools to recommend the right diet at the right time for a specific patient with a specific disease, health, and personal and social characteristics [111].

Future high-powered studies on dietary strategies based on a precision nutrition framework are needed better to understand the mechanisms behind the therapeutic effects of food and to enable clinicians and dietitians to design an ultra-personalized dietary plan for patients. This can translate into better- and higher-quality management of IBD.

Author Contributions

Conception: Paula Ministro. Drafting of the manuscript: Caroline Soares. Critical revision: Paula Ministro. Approval of the final: Paula Ministro and Caroline Soares. Guarantor of the article: Paula Ministro.

Competing Interests

The authors have declared that no competing interests exist.

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