Optimizing Nutrition to Enhance the Treatment of Patients With Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) consists of chronic, relapsing-remitting autoimmune diseases of the gastrointestinal (GI) tract with an increasing global disease burden. Pathogenetic mechanisms are not well understood, but current hypotheses involve the role of environmental factors, including dietary antigens, in immune dysregulation and proinflammatory shifts in microbial composition (gut dysbiosis) in genetically susceptible individuals. Increased metabolic demand and malabsorption secondary to systemic inflammation, coupled with significant GI symptoms that lead to reduced oral food intake, may leave patients with IBD vulnerable to developing malnutrition. The use of diet as therapy for potential induction or maintenance of remission in IBD has risen to prominence in the past several decades, especially as patients explore diet as a means to improve their symptoms and overall quality of life. However, these nutritional therapies remain underutilized by many gastroenterologists, and randomized controlled trials (RCTs) for most popular diets are lacking. Moreover, formal and consistent assessments of the nutritional status of patients with IBD in the inpatient and outpatient settings are often overlooked. To address these gaps, this article aims to discuss the progress of diet therapy and considerations for optimizing nutrition in patients with IBD, as well as summarize current RCTs evaluating efficacy for the most popular diets in IBD therapy.

Keywords
Crohn's disease, ulcerative colitis, inflammatory bowel disease, diet, malnutrition

Inflammatory bowel disease (IBD) primarily consists of Crohn's disease (CD) and ulcerative colitis (UC), which are chronic, progressive, relapsing-remitting diseases that largely involve the gastrointestinal (GI) tract. Although once considered a medical condition of developed nations, rising IBD incidence in the past several decades has been noted in newly industrialized countries in Asia, Southeast Asia, the Middle East, and South America, indicating a rapidly expanding global disease burden.[1] Traditional IBD therapy involves the use of anti-inflammatory drugs, including corticosteroids, aminosalicylates, immunosuppressing

agents such as thiopurines, and gut-specific and systemic biologic agents to induce endoscopic and clinical remission and prevent disease progression.[2]

The use of diet in the management of IBD has progressed in the past several decades but still remains incompletely understood and underutilized by many clinicians, despite posing several advantages. Ideally, the use of diet to treat IBD would help with symptom control, improve quality of life, improve nutritional deficiencies, and, importantly, lessen side effects of chronic immunosuppressive therapies (eg, ensuring adequate calcium intake for patients on corticosteroids).[3] Moreover, given that symptoms during active states and remission predispose patients to malnutrition, the role of diet in IBD treatment is paramount in the inpatient and outpatient settings.

Nutritional deficiencies are frequent in both the active and quiescent disease states because of multiple causes, including decreased oral food intake owing to active symptoms, increased metabolic demand owing to systemic inflammation, malabsorption owing to gut inflammation, and nutritional losses through diarrhea.[4] The risk of nutritional derangements is greater in CD given its potential for extensive involvement of the GI tract, particularly the small bowel. In a prospective study of 333 patients with CD or UC, the prevalence of malnutrition was 16% (95% CI, 12%-20%), with increased risk with active disease, history of abdominal surgery, or self-imposed restriction of foods perceived to worsen flare symptoms.[5] In hospitalized patients, malnutrition is associated with prolonged length of stays, higher rates of complications including infections, increased readmission rates, and increased mortality.[6] Baseline nutritional status may worsen in IBD inpatients owing to iatrogenic lack of feeding because of protocols or inappropriately long periods of bowel rest. Thus, early recognition of malnutrition and a foundational understanding of nutritional interventions have the potential to improve both short- and long-term patient outcomes.[7]

From the patient perspective, food and nutrition are integral parts of daily life. Understandably, patients with IBD often seek recommendations from their health care providers to control their disease through diet, especially given the inherent involvement of the GI tract in their disease process. In a national health care provider and patient survey, Tinsley and colleagues found that patients attributed more importance to nutrition strategies in the management of their IBD and less importance to medications, compared with physicians. Moreover, although gastroenterologists thought that nutrition was important in IBD, only 65% (131/202) screened patients for malnutrition during visits, and 41% (91/223) thought they had access to adequate nutritional resources to guide their patients in discussions regarding diet.[8] As a result, patients often turn to alternative sources of information such as the Internet, which may result in overly restrictive diets in individuals who are at risk for onset or progression of malnutrition.

To fill these gaps, this article discusses the progress of diet therapy in IBD, provides guidance to the clinician on screening for malnutrition in patients with IBD, and examines current popular diets in IBD therapy and their associated trials.

Progress of Diet Therapy in Inflammatory Bowel Disease

Early historical approaches of medical therapy in IBD were representative of the broad-based misconceptions of human illness. In the 1900s, treatment of IBD included slop diets, antiseptics, astringents, milk soured by lactic acid, and kerosene, with desperate hopes to cure patients of their diarrhea and associated symptoms.[9,10] With increased economic development and food production, as well as rapid population increases with industrialization in the Western world, the incidence of IBD in resource-rich countries rose exponentially in the late 20th century.[1] Understanding of IBD improved with concurrent advances in immunology, molecular biology, and genetics, as well as the advent of randomized controlled trials (RCTs).

Despite rising incidence and medical advancements, the exact etiology of IBD remains to be explained. Current hypotheses involve the role of one or multiple environmental factors triggering inflammatory pathways in the gut in genetically susceptible individuals.[11] The normal gut microbiome physiologically contributes to nutrition, metabolism, immunity, and host defense against external pathogens. Unfavorable alterations in the intestinal and colonic microbiota, known as gut dysbiosis, have been implicated in the pathogenesis of IBD. These shifts in microbial composition, as well as dysregulation of the intestinal immune system, are thought to contribute to altered host responses, impaired barrier function, increased mucosal inflammation, and alteration of mucosal permeability.[12]

Dietary antigens and their interaction with the gut microbiome are thought to play significant roles as potential environmental factors, although a causal relationship between diet and IBD development has not been established.[13] In particular, Westernization of diet has been implicated in IBD development, with the highest incidence and prevalence of disease in North America and Europe.[14] Vangay and colleagues demonstrated that migration from a non-Western to a Western country can cause pronounced shifts in the individual microbiome

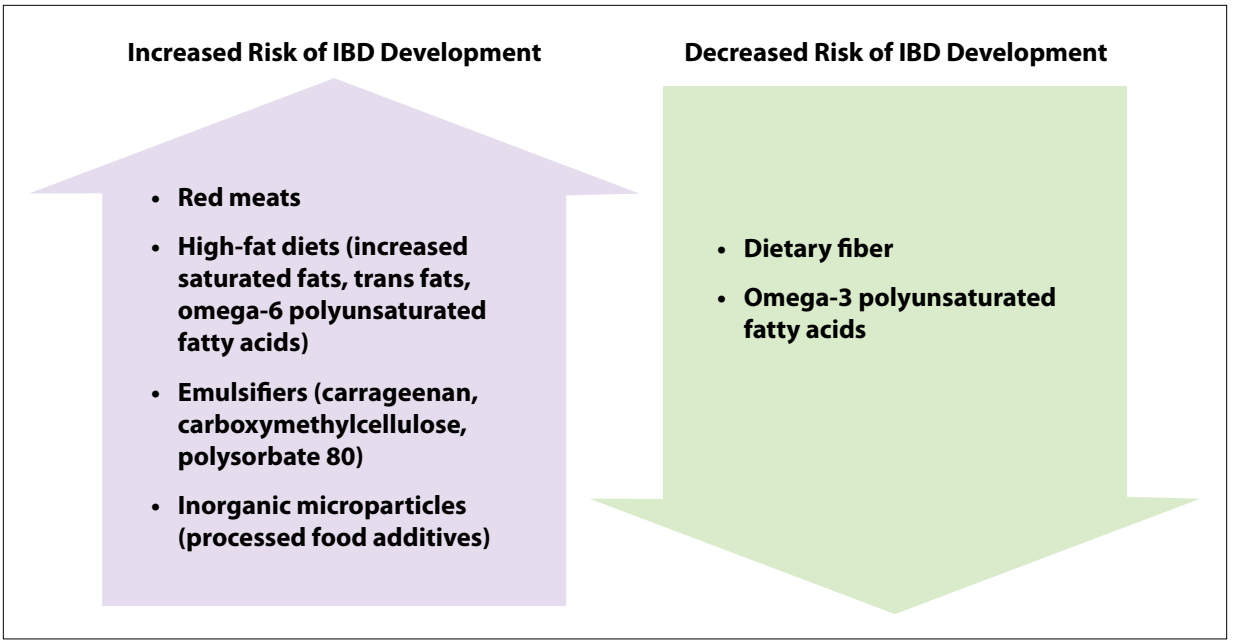

Figure. Food components associated with increased or decreased risk of IBD development.
IBD, inflammatory bowel disease.

and that microbial diversity decreases with each generation of residence.[15]

Certain food additives and nutrients have been specifically associated with increased risk of disease (Figure).[16] Hou and colleagues' systematic review of 19 studies with 2609 IBD patients (1269 CD/1340 UC) and more than 4000 controls for pre-illness intake of nutrients and risk of IBD development demonstrated a positive association of intake of meat and total fats, including saturated fats, monounsaturated fatty acids, polyunsaturated fatty acids, and omega-6 fatty acids, with an increased risk of developing CD and UC.[17] This study also demonstrated a negative association between fiber intake and fruits in CD and UC risk. Further studies have demonstrated anti-inflammatory properties of n-3 polyunsaturated fatty acids within in vivo and in vitro experimental models.[18,19]

Improved understanding of possible pathologic mechanisms of disease in the interactions between dietary antigens and the microbiome has guided the creation of treatment modalities regarding diet. Specifically, nutritional therapy assumes that shifting the microbiome toward a less proinflammatory profile by reducing exposure to proinflammatory antigens (additives, meats, emulsifiers) with the addition of protective agents (fiber, omega-3 fatty acids) could decrease intestinal inflammation.

As such, diet therapy as a form of nonpharmacologic treatment has become increasingly prominent in the past several decades, and by some medical societies it is now considered primary or adjunct treatment of active IBD rather than only supportive therapy, especially for CD in pediatric populations.[20]

However, there are currently few prospective trials for the various types of diet therapy, and those trials are often not blinded, have low patient sample sizes that may not be powered enough to detect significant differences between standard therapies, or rely on symptom scores rather than objective markers of active disease such as inflammatory markers or endoscopic evidence.[21] Currently, the lack of large prospective trials may not provide the evidence for diet therapy that patients and physicians desire, but diet therapy shows promise in providing symptom relief.

Optimizing Nutrition for Patients With Inflammatory Bowel Disease

A major concern in treating patients with IBD is the prevention and treatment of malnutrition.

Untreated malnutrition may worsen the prognosis, complication rates, mortality, and quality of life of patients with IBD.[22] Factors contributing to malnutrition in IBD include reduced oral food intake secondary to symptoms or self-imposed restrictive diets, malabsorption, increased nutrient losses from the gut (fluid and electrolyte losses and protein-losing enteropathy), drug-nutrient interactions, and increased metabolic and nutrient requirements.[23,24] One study documented weight loss in 70% to 80% of hospitalized IBD patients and in 20% to 40% of outpatients with CD.[25] Several

Table 1. Malnutrition Screening and Assessment Tools With Abbreviations That Have Been Suggested for Use in Inflammatory Bowel Disease Patient Populations

Nutrition Screening Tools	Nutrition Assessment Tools
• Nutrition Risk Screening 2002 (NRS-2002) • Malnutrition Universal Screening Tool (MUST) • Nutritional Risk Index (NRI) • Malnutrition Inflammation Risk Tool (MIRT) • Saskatchewan Inflammatory Bowel Disease Nutrition (SaskIBD-NR)	• Subjective Global Assessment (SGA)[76] • American Society for Parenteral and Enteral Nutrition (ASPEN) assessment tools[77] • Global Leadership Initiative on Malnutrition (GLIM) criteria

factors should be considered in assessing malnutrition risk in IBD patients in both inpatient and outpatient settings, which are summarized in the following section.

Assessing Nutritional Status

Screening and assessment tools should be routinely implemented in order to properly screen and diagnose malnutrition in the patient with IBD. Nutrition screening tools are used first line and involve 2- to 3-question assessments completed by nurses or doctors (Table 1).[26] Nutrition assessment tools are more comprehensive evaluations that utilize metrics such as muscle loss, fat loss, energy intake, and weight loss (also known as the Nutrition-Focused Physical Exam) to make the diagnosis of malnutrition. Regardless of the method used, screening should be performed routinely for all patients with IBD admitted to the inpatient setting and should be performed periodically at outpatient follow-up visits.

Additionally, albumin and prealbumin are often used to determine nutritional status in hospitalized patients with IBD. However, as serum concentrations of albumin and prealbumin decline in the presence of inflammation, low concentrations of albumin or prealbumin should not be used as a sole indicator of nutrition status but instead considered in conjunction with the aforementioned assessment tools (Table 1).[27]

One major challenge in addressing nutritional status in IBD involves a current lack of standardized screening protocols that specifically address the needs of patients with IBD. Fortunately, the Crohn's & Colitis Foundation (CCF) IBD Qorus recently published a proposed nutrition care pathway that recommends Malnutrition Universal Screening Tool (MUST) screening of patients to help health care providers categorize patients as low, moderate, or high risk for malnutrition, which then triages patients for the necessity and urgency of more detailed assessment and intervention by a dietitian.[28] As the MUST tool is validated primarily for use in hospitalized patients, Hwang and colleagues pilot tested components within the CCF IBD Nutritional Care Pathway utilizing a modified MUST (known as mMUST) tool that is applicable in the outpatient setting and has the advantage of being self-administered by patients.[29]

Pharmacologic and Surgical Treatments

Drug-nutrient interactions and medication side effects may cause impaired digestion and absorption of nutrients. Side effects from immunosuppressive drugs and biologic agents, especially thiopurines, include nausea and GI upset, which could contribute to decreased appetite and poor oral food intake.[30] Glucocorticoids are associated with the reduction of intestinal calcium absorption and increased excretion of renal calcium.[31] Folate deficiency is associated with methotrexate and sulfasalazine.[32] Additionally, surgical resections of the small bowel can reduce the absorptive area of the intestine, increasing risk of malabsorption and vitamin B_{12} deficiency, depending on the extent of the resection.[30] With the proper management of side effects, micronutrient supplementation, and diet interventions, these complications can be reduced.

Inappropriate Inpatient Nothing by Mouth Orders

Many clinicians empirically advise patients with IBD to fast when hospitalized with severe flare-ups. However, in the absence of contraindications to feeding, there is currently no evidence to support that maintaining complete bowel rest improves disease course. In a retrospective study of 222 patients admitted with IBD, no significant difference was noted in disease activity reduction between patients fasting and patients placed on an oral diet upon admission, emphasizing that oral diet should not be avoided unless not tolerated by the patient.[33] Contraindications to feeding include bowel obstruction, uncontrolled sepsis, and the need for urgent or emergent surgery; otherwise, patients should be fed in whatever capacity tolerated. Moreover, penetrating or stricturing disease is not necessarily a contraindication to feeding; patients may benefit from consuming an oral diet as

Table 2. Diets Used for Augmenting Treatment in IBD, Populations in Which to Consider Use, Prospective Trials, and Additional References

Diet	Population(s) in Which to Consider Use, Based on Evidence	Prospective Trials and Additional References
Exclusive enteral nutrition	Active (mild to moderate) pediatric CD	• Swaminath et al (2017): meta-analysis of pediatric CD, n=451[41] • Narula et al (2018): meta-analysis of adult and pediatric CD, n=223; notably, very low evidence supports that corticosteroids are more effective than exclusive enteral nutrition in induction of remission in adults with CD[38] • CD-TREAT (2019)[54] • Levine et al (2019)[55]
Specific Carbohydrate Diet	Active (mild to moderate) pediatric and adult CD	• Cohen et al (2014)[71] • PRODUCE (2021)[60] • DINE-CD (2021)[58]
Mediterranean diet	Active (mild to moderate) adult CD	• DINE-CD (2021)[58]
Low-FODMAP diet	Inactive CD and UC with underlying functional GI symptoms	• Halmos et al (2016)[67] • Pedersen et al (2017)[68] • Bodini et al (2019)[69] • Cox et al (2020)[70]
CD Exclusion Diet	Active (mild to moderate) pediatric CD	• Levine et al (2019)[55]
Semi-vegetarian diet	Active (mild to moderate) adult CD	• Chiba et al (2010): prospective, uncontrolled trial[72] • FACES trial (2019): negative study[73]
Low-fat diet	Inactive or mild adult UC	• Fritsch et al (2021)[74]
Paleolithic diet	Unclear IBD population	• Unproven; no data available
IBD anti-inflammatory diet	Possibly inactive or mild adult CD or UC	• No RCTs • Olendzki et al (2014): case series[75]

CD, Crohn's disease; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide, and polyol; GI, gastrointestinal; IBD, inflammatory bowel disease; RCT, randomized controlled trial; UC, ulcerative colitis.

tolerated with enteral and/or parenteral nutrition supports used as needed to supplement nutrition.[34]

Current Dietary Interventions in Inflammatory Bowel Disease

There are quite a few dietary therapies proposed to modify disease activity, with varying quality of evidence to support their efficacy. The best-studied diets are discussed in the following sections, with emphasis on proposed mechanism of action, dietary recommendations, and prospective clinical trials supporting their use (Table 2).

Of note, for defined or exclusion diets (ie, dietary regimens that restrict certain types of foods), partnership with a registered dietitian is strongly recommended when initiating and maintaining these dietary interventions, as eliminating various foods and food groups may predispose patients to nutrient deficiencies. Nazarenkov and colleagues' dietary comparisons using recommendations from the US Department of Agriculture and CCF evaluated 8 defined diets (including the Specific Carbohydrate Diet [SCD]; low–fermentable oligosaccharide, disaccharide, monosaccharide, and polyol [FODMAP] diet; and CD Exclusion Diet [CDED]), and showed that most of the diets (7/8) were associated with inadequate iron intake in women or failed to meet the recommended intake of vitamin D and calcium; 3 of the 8 diets were deficient in omega-3 and zinc.[35]

Exclusive Enteral Nutrition

The nutritional intervention with the strongest evidence of inducing clinical and endoscopic disease remission in IBD, particularly in CD, is the use of exclusive enteral nutrition (EEN).[36,37] With EEN, patients obtain all of

their nutrition through liquid preparations (ie, formula) for approximately 4 to 12 weeks via oral or feeding tube formulas.

The formulations of EEN vary based on protein content and structure. Elemental formulations contain amino acids without intact protein and require administration via nasogastric tube. Semi-elemental diets are comprised of oligopeptides and, like elemental formulations, usually require nasogastric administration owing to distaste and intolerability. Polymeric diets contain whole proteins and can be better tolerated orally.[20] There are no significant differences in rates of induction of remission among elemental, semi-elemental, and polymeric formulations in both pediatric and adult populations.[38-40]

To date, multiple RCTs have compared the efficacy of EEN with traditional corticosteroid therapy in active disease.[38,41-45] Among meta-analyses that evaluated these studies, overall consensus remained mixed, but EEN has demonstrated efficacy equal to corticosteroids in reducing remission by promoting mucosal healing in exclusively pediatric populations.[46] Proposed mechanisms of EEN are still being elucidated, but multiple anti-inflammatory mechanisms, including a reduction in proinflammatory cytokines and changes in the microbiome, are hypothesized to be secondary to decreased antigenic load from removal of a regular diet.[47-49] EEN has the advantage of repleting nutritional deficits and addresses malnutrition with few side effects, which include GI upset such as nausea, vomiting, diarrhea, heartburn, and flatulence; rare cases of refeeding syndrome have been reported.[41,50]

Collectively, the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, and the European Crohn's and Colitis Organisation consider EEN first-line therapy for induction of remission in pediatric CD,[51] with rates of approximately 60% to 85%.[52] EEN is noted to be most effective with small bowel disease and does not appear to be effective in patients with UC.[53] Moreover, data for EEN utilization in adults are less conclusive, owing to decreased tolerability and refusal for nasogastric food preparations, especially with prolonged use.

To counter issues with palatability and sustainability of EEN, 2 recent RCTs, CD-TREAT and Levine and colleagues' CDED trial, aimed to achieve the therapeutic results of traditional EEN through whole foods with a similar composition to EEN (and in the case of CDED included partial enteral nutrition with 25% to 50% of consumed calories derived from an enteral formula).[54,55] These studies show promise in inducing disease remission while demonstrating improved oral tolerance to enteral diets and may help their eventual adoption in adult populations.

Specific Carbohydrate Diet

The SCD was first implemented by pediatrician Dr Sidney Haas in the 1950s for the treatment of children with celiac disease. It was further popularized for use in IBD by Elaine Gottschall's book *Breaking the Vicious Cycle: Intestinal Health Through Diet* in 1994, where she discusses cure of her daughter's UC with the use of the SCD for 2 years.[9] The concept behind the SCD is that diseases such as IBD are owing to intestinal injury caused by an overgrowth and imbalance of proinflammatory gut microbes from consuming poorly absorbed carbohydrates, specifically disaccharide and polysaccharide carbohydrates.

The SCD allows for carbohydrates consisting of monosaccharide carbohydrates, such as glucose, fructose, and galactose, as well as proteins and fats.[56] Thus, this diet recommends that patients avoid most grains, such as wheat, barley, corn, and rice, processed/canned foods, and milk, but allows most fresh fruits and vegetables, meat, yogurt, nuts, and hard cheeses. Although highly restrictive, studies have shown rates of high adherence to the diet. Kakodkar and colleagues' 50-patient case series demonstrated a mean adherence rate of 95% with the SCD with a mean duration of 35 months.[56] Additionally, Suskind and colleagues' survey of 417 IBD patients reported 96% perceived adherence to the SCD with a mean duration of 32 months.[57]

Most studies performed to evaluate the SCD have been retrospective observational studies or survey studies in pediatric populations with CD; however, the recent prospective trial DINE-CD, which compared the SCD with the Mediterranean diet, demonstrated symptomatic remission in more than 45% of adult patients with mild to moderate CD but with only 5% demonstrating an associated decrease in inflammatory markers after 6 weeks on the diet (Table 2).[58] The PRODUCE trial, a randomized crossover study that compared the effectiveness of strict SCD with a liberalized, modified SCD in reducing symptoms and inflammatory burden in 54 pediatric patients, also found that the SCD improved GI symptoms, with no differences in outcomes found between a modified and a strict diet, suggesting that a more liberal approach to the SCD may be effective.[59,60]

Mediterranean Diet

The Mediterranean diet is based on the diet traditionally followed in southern France, Italy, and Greece, and is centered around a diet high in fruits and vegetables, moderate whole grains, and proteins from fish, poultry, and beans, with olive oil as the principal oil. The proposed mechanism of this diet is that high consumption of foods rich in oleic acid (olive oil) and omega-3 fatty acids that have anti-inflammatory properties and higher fiber may contribute to favorable gut microbiota shifts.[61]

Recent support for this diet in IBD has included epidemiologic studies associating lower risk of developing IBD with consuming a Mediterranean diet, as well as uncontrolled studies showing improved quality of life and lower degrees of intestinal inflammation after diagnosis if consuming this diet.[62-64] The aforementioned DINE-CD trial provided prospective, controlled data comparing the Mediterranean diet with the SCD, in which both diets appeared equally efficacious in improving GI symptoms and quality of life, suggesting that avoiding certain dietary elements such as processed foods and increasing intake of whole foods such as fruits and vegetables may be more important than adhering to a specific, restrictive dietary regimen.[58]

Low-FODMAP Diet

Traditionally, the low-FODMAP diet, which limits the intake of fermentable, poorly absorbed short-chain carbohydrates (oligo-, di-, and monosaccharides) and polyols, has been utilized in the treatment of irritable bowel syndrome (IBS) and functional GI symptoms.

In many IBD patients with minimal disease activity or remission, GI symptoms may persist and may be reflective of an underlying IBS or functional GI disorder; the significant symptom overlap between IBD and functional GI disorders poses treatment challenges for the health care provider and patient.[65,66] As such, RCTs that evaluate the use of the low-FODMAP diet focus assessments on symptomatic improvement in patients with quiescent or mild disease, as this diet aims to improve functional GI symptoms rather than impact inflammation in IBD (Table 2).[67-70]

The low-FODMAP diet is comprised of a strict reduction phase of all dietary FODMAPs for a period of 2 to 4 weeks, followed by a reintroduction phase of FODMAPs based on the patient's symptoms and tolerance. A low-FODMAP diet, particularly the elimination phase, is not meant to be instituted as long-term therapy, as this may predispose patients to micro- or macronutrient deficiencies. Moreover, the restrictive nature of the diet, especially if reintroduction phases are prolonged, may create problems with adherence for the patient over time.

Conclusion

As the prevalence of IBD continues to increase, more patients may present to their health care providers seeking to learn about the role of nutrition in the management of their IBD. Several questions remain, but health care providers should feel empowered to counsel their patients on what is known thus far, including: (1) No exact food or environmental factor is known to directly cause IBD or induce flares; however, current hypotheses involve the role of dietary antigens in gut dysbiosis and immune dysregulation, forming the basis of nutritional therapies in IBD management. (2) Given worse short- and long-term outcomes associated with malnutrition states, nutrition screening should be a standard part of care for all IBD patients. Furthermore, patients should be encouraged to consume an oral diet when hospitalized for IBD unless clear contraindications are present. (3) Given multiple risk factors for malnutrition in IBD and risk of macro- and micronutrient deficiencies associated with specialized diets, gastroenterologists should strongly consider utilization of registered dietitians in optimizing nutrition in IBD in the inpatient and outpatient settings. Currently, no one standardized screening protocol specific to IBD patients exists, but IBD nutrition care pathways, such as that from the CCF, provide the best guidance to date for health care providers. (4) Current evidence suggests no clear dietary recommendations for any specific diet in IBD therapy except for EEN in pediatric CD populations; for most popular diets, prospective trials are lacking, and those available are open-label trials with small sample sizes. However, recent data are promising, with a shift toward incorporation of whole foods into diet. With whole foods, more palatable dietary choices are offered to the patient, which may lead to improved adherence and in turn may contribute to subjective symptom relief and decreased objective burden of inflammation.

Disclosures

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