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REVIEW

Importance of nutrition in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) results from the interaction between an individual's immune response and precipitant environmental factors, which generate an anomalous chronic inflammatory response in those who are genetically predisposed. Various feeding practices have been implicated in the origin of IBD based on epidemiological observations in developed countries, but we do not have solid evidence for the etiological role played by specific food types. IBD is associated with frequent nutritional deficiencies, the pattern and severity of which depends on the extent, duration and activity of the inflammation. Nutritional support allows these deficiencies in calories, macro- and micro-nutrients to be rectified. Enteral nutrition is also a primary therapy for IBD, especially for Crohn's disease, as it allows the inflammatory activity to be controlled, kept in remission, and prevents or delays the need for surgery. Nutritional support is especially important in childhood IBD as an alternative to pharmacological treatment. This report discusses the complex relationship between diet and IBD.

Key words: Nutritional support; Inflammatory bowel disease; Enteral diet; Crohn's disease; Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a heterogeneous group of chronic diseases of unknown etiology, unclear pathogenesis and a systemic nature that cause inflammation of the digestive tract, and includes Crohn's disease (CD) and ulcerative colitis (UC), which are traditionally found at opposite ends of the disease spectrum. While UC is exclusively restricted to the large bowel, CD can virtually affect any segment in the digestive tract, and may even be accompanied by extraintestinal manifestations. All diseases in the group involve alteration of the immunological tolerance system of the digestive tract mucosa[1], triggered by a certain factor which gives rise to an inappropriate, serious and prolonged inflammatory response in genetically predisposed individuals[2,3]. The ultimate causes of IBD have not yet been identified, but epidemiological studies show differences in the rate of IBD in terms of age and onset, race and geographical areas[4,5]. The existence of environmental factors is therefore suggested, which are capable of substantially altering the appearance of CD and UC. Among these, smoking and appendicectomy are the most notably implied, but the possible etiological role in the disease played by oral contraceptives, perinatal and childhood infections, or infections caused by atypical mycobacteria and diet has also been highlighted.

Various dietary and nutritional factors have been suggested as being significant etiological factors both for CD and UC[6], but at the same time, and more importantly, nutrition itself has proven to be a central component in the treatment of the disease, both as a primary therapy and for correcting the various nutritional deficiencies shown by these patients[7]. This report addresses these matters through a literature review, adding certain recommendations for the nutrition management of patients with IBD in the light of the evidence available.

DIET IN IBD

IBD results from the interaction of three essential co-factors: genetic susceptibility, environment and the immune response of the individual[8]. Environmental

factors may include both the local microenvironment (enteric microflora), and the nutritional environment. We do not have definitive data to demonstrate that diet is a cause of CD or UC, but over the past few decades, numerous studies have highlighted the potential etiological role played by certain feeding practices, based on the proportional increase of the incidence of IBD in developed countries and the appearance of new feeding habits in these regions[4]. New lifestyles include new feeding habits in which the consumption of cow's milk by children, the consumption of high quantities of refined sugar and fat and the low consumption of dietary fiber, fruit and vegetables take precedence.

Several studies have shown that breastfeeding reduces the possible development of UC[9-11] and CD[11-13]. Even in the case of infants who were breast fed for a short period of time, the risk of CD was significantly increased compared to the group that was breast fed for a longer time[12]. The consumption of cow's milk has also been implicated in the etiology of IBD[14], and these patients were shown to have higher levels of serum antibodies against cow's milk protein compared to healthy controls[15], with a correlation between the levels of specific antibodies and the index of activity in the case of adults with CD[16]. The relationship between breastfeeding and IBD has not been observed in other studies but various assumptions provide explanations as to the protective mechanisms of breastfeeding against IBD including: protection provided by breast milk against gastrointestinal infections[17-19]; its ability to stimulate the development of the gastrointestinal mucosa and its immunological capacity in children[20-23]; or postponing contact with cow's milk and other allergens and potentially infectious agents. Recently, the possible etiological role of *Mycobacterium avium paratuberculosis* as being an infectious agent which causes CD has been suggested[24,25]; this organism, originating from infected cows, could be transmitted through the milk and resist pasteurization[26]. However, several arguments against the putative role of *M. avium paratuberculosis* in causation of CD have been given, such as the lack of epidemiological support for transmissible infection, the absence of therapeutic benefit of traditional antimycobacterial antibiotics, and the low incidence of IBD in developing countries[27].

New feeding habits involve a high consumption of sugar and refined carbohydrates. Since the 1970s, various studies have indicated the high consumption levels of these products in patients with IBD[28,29], to the extent that they are now considered a risk factor for CD[30-32] and UC[31,33-35]. Conversely, the consumption of citrous fruit, fruit juices and vegetables could lower the risk[36] of the development of both diseases[37-39], and a particular study even showed an inverse relationship between the consumption of bran and the onset of CD[40]. To date, it has been impossible to determine whether the potentially protective effect is due to the action of the fiber or to other micronutrients contained in fruit and vegetables. The utility of low refined carbohydrate diets in the treatment of CD has been suggested by several authors[32,34], although extensive clinical trials have not confirmed the benefits of this measure[41].

In recent years, special attention has been paid to the lipid components of the diet as triggers of IBD. Since the earliest epidemiological relationships were demonstrated between the consumption of partially hydrogenated fats (margarine) and granulomatous ileitis[42] and UC[43], various studies have shown that new consumption patterns, such as fast food, could be linked to an increased risk in the development of CD and UC[36,44]. In addition, the consumption of large amounts of monounsaturated and polyunsaturated fats are both associated with a higher risk of UC[45,46]. The observation that the Eskimos in Greenland, consumers of large quantities of n-3 polyunsaturated fatty acids (PUFAs) deriving from fish oils, had a low prevalence of IBD[47,48] led to the study of the anti-inflammatory properties of n-3 PUFAs[49], in comparison with pro-inflammatory n-6 PUFAs. The latter have been clearly implicated in the origin of IBD, given that they affect the arachidonic acid metabolism by increasing the production of leukotriene B4, with pro-inflammatory action. These discoveries have opened up new channels of knowledge regarding the ability of lipids in the diet to regulate inflammatory processes in different diseases, as they are the fundamental component of cell membranes, including those of lymphocytes, which orchestrate immune system responses[50].

Short-chain fatty acids (SCFAs), of which butyrate is the most representative, are particularly worthy of note and are generated during the colonic fermentation of dietary fiber and other unabsorbable carbohydrates. A quantitative SCFA deficiency or their oxidation by colonocytes have been implicated in the physiopathology of UC[51,52], and SCFA *in vivo* oxidation is also lower in affected patients[53].

With regard to the protein and calorie intake in the diet, some studies have suggested that the intake of proteins[46,54] and calories[54] might be higher in patients with IBD compared to controls, although these data have not been uniformly observed and we do not know whether these factors are a cause or a consequence of the disease.

Despite the data presented at this moment in time, we still lack solid evidence regarding the accountability of certain dietary components in the etiology of IBD, although the aforementioned data oblige us to consider that the changes in the composition and characteristics of the diet which typifies modern life have been accompanied by substantial changes in the epidemiology of IBD in developed counties. However, we must remember that, beyond diet, our current lifestyle also has other characteristics whose possible etiological role in IBD has not been studied in depth.

NUTRITIONAL DEFICIENCY IN IBD

From the earliest descriptions of the disease, IBD,

especially CD, has been traditionally associated with serious nutritional deficiency. The pattern and severity of malnutrition in IBD depends on the duration, activity and extent of the disease, with significant differences having been described between CD and UC, given that the involvement of the small intestine is accompanied by a higher incidence of protein-calorie malnutrition and deficiencies in specific nutrients[55]. Furthermore, CD presents considerable chronic deficiencies, whereas in UC, the nutritional status tends to be more preserved, although during the flares of activity of the disease and in cases of hospitalization, the deficiencies tend to be significant[56]. In accordance with the methods and criteria considered for diagnosis, between 20% and 85% of IBD sufferers have nutritional deficiencies with prominent calorie-protein malnutrition in CD and protein malnutrition in UC[57]. A high proportion of CD patients (between 25% and 80%) and UC patients (between 25% and 50%) present hypoalbuminemia during hospitalization[55,58], which may clinically manifest as weight loss.

The origins of malnutrition in CD are multifactorial, but dietary restrictions (due to intolerance of diet or therapeutic fasting) are the most important. Also included are: the increase in energy requirements[59-61], the malabsorption of nutrients in the case of extensive intestinal involvement, gastrointestinal losses and the interaction between nutrients and drugs. Furthermore, the underlying inflammatory mediators of the physiopathology of IBD[62], such as tumor necrosis factor (TNF)-α, and interleukins-1 and -6 can increase catabolism and lead to anorexia. Table 1 provides a summary of the causes of malnutrition in IBD[63].

Table 1 Causes of malnutrition in IBD (modified from García-Manzanares *et al*[63])

Decrease in oral intake	Restrictive diets, therapeutic fasting
	By the disease itself: diarrhea, abdominal pain, nausea and vomiting, *etc*
	Alteration in taste: due to drugs, vitamin and mineral deficiencies, pro-inflammatory mediators
	Anorexigenous effect of pro-inflammatory cytokines
Gastrointestinal losses	Diarrhea
	Rectorrhagia/hematochezia
	Loss of mucus and electrolytes
	Protein-losing enteropathy
Metabolic disorders	Increase in resting energy expenditure
	Enhanced fat oxidation
Increase in nutritional requirements	Inflammatory states
	Increased basal oxidative metabolism
	Infectious complications
	Post-surgery
Drug interaction	Corticoids and calcium reabsorption
	Corticoids and protein catabolism
	Salazopirine and folates
	Methotrexate and folates
	Cholestyramine and liposoluble vitamins
	Antimicrobials and vitamin K
	Anti-secretors and iron
Poor absorption of nutrients	Reduction of the absorptive surface: intestinal resection, enteric fistulas, hypertrophy of the villi
	Blind loops, bacterial overgrowth
	Poor absorption of bile salts in ileitis or resection

Although micronutrient deficiency in IBD is common, in most cases it does not tend to have any evident clinical manifestation, except with regard to iron, folic acid, and vitamin B12[57]. However, those micronutrients which have an impact on bone mineral density, thrombophilia or carcinogenesis are of significant clinical interest. Little is known about other micronutrient deficiencies in IBD in terms of their consequences, frequency and subclinical development, due to the lack of studies in this area. However, many of them could be involved in regulating immune response at different levels[64].

IBD patients show an increased loss of bone mass[65,66], which could lead to osteopenia and osteoporosis, and which in certain studies, affects up to half the number of patients with CD and UC[67,68] and contributes to an increased risk of fractures up from 40% to 60%[60]. Although multifactorial in origin, the action of certain pro-inflammatory cytokines (especially TNF-α) has recently been highlighted with respect to bone loss[67]. Aside from the chronic or recurring use of corticosteroids[69], age, the female gender, type of IBD, smoking and other hormonal and genetic factors also contribute to osteoporosis in IBD[67].

Folic acid deficiency observed in half the number of patients with IBD might be due to difficulties in swallowing (low-fiber diets), poor absorption or competitive inhibition by certain treatments, such as sulphasalazine or methotrexate[63]. The absence of folic acid has been related to the increased risk of colitis-associated carcinogenesis[55,70], as it has a protective effect against high-grade dysplasia and cancer in patients with long-term UC[71,72]. Folate deficiency is also linked to the increased incidence of arterial and venous thromboembolic events observed in CD and UC[73], due to hyperhomocysteinemia, a well-known inducer of hypercoagulability states. Both folic acid and vitamin B12 are essential co-factors in the metabolic route of homocysteine-methionine[74]. Between 20% and 60% of patients with CD and terminal ileitis are deficient in vitamin B12.

Other relevant nutritional deficiencies in CD are iron, zinc or selenium. Zinc is a vital component for the healing of wounds and its deficiency should be considered in the case of recurrent fistulous disease[75,76]. In addition, zinc is a co-factor of superoxide dismutase, which protects against cell damage caused by free radicals. Selenium is a co-factor of glutathione periodoxase[63]. Oxidative stress is one of the factors which perpetuates the inflammatory response in IBD[77], which is why a sufficient intake of antioxidant agents such as vitamins A, C, E and selenium is of extreme importance and has been inversely correlated with the plasma levels of pro-inflammatory agents[77,78].

Malnutrition has particularly serious direct consequences for patients with IBD. The scope thereof

depends on various factors, noteworthy being the age at which the disease begins and its activity. Delayed growth in children is the most frequent extraintestinal manifestation[79]; it is detected early and affects 75% of patients with CD and 10% of cases of UC[63]. Various pro-inflammatory cytokines, which are frequently high in IBD[80], are involved in the growth retardation and puberty of these children, as well as absorption deficiencies or increased catabolism. The objectives in the treatment of these patients should be aimed at acquiring knowledge of the inflammatory mechanisms and the control of their effects using immunomodulatory and biological treatments and at optimizing nutritional treatment[81], which frequently requires coordination among gastroenterologists, endocrinologists and nutritionists.

Calorie-protein malnutrition causes humoral and cellular immunodeficiency. Its effects on the intestine lower the efficiency of the mucosal barrier, lead to alteration of the functionality of the mucosa-associated lymphoid tissue and to a greater risk of infection by bacterial translocation. Hypoplasia of the intestinal villi perpetuates malabsorption and increases the risk of infections.

Metabolic bone disease develops silently in these patients, the origin of which is probably multifactorial[82]: steroids, lack of physical activity, deficiencies of calcium, vitamins and other micronutrients and alterations of the intestinal villi.

NUTRITION AS AN EFFICIENT PRIMARY TREATMENT IN IBD

Nutrition therapy should play a fundamental role in the clinical management of all patients with IBD. Its objectives are to correct macro and micronutrient deficiencies in frequently malnourished patients subject to increased oxidative catabolism, to reverse the physiopathological consequences of such deficiencies, and also to exert its own anti-inflammatory therapeutic effect.

Enteral feeding using formulas or liquids should always take preference over parenteral feeding, unless it has been completely contraindicated. If oral feeding were not possible, feeding the patient through a nasogastric or nasoenteric tube should be considered. The value and benefits deriving from its use are directly dependent on the geographical location of the disease, its extent and gravity and enteral feeding is therefore especially indicated for CD patients when the small intestine is affected, while there is no evidence which supports the use of enteral nutrition in the treatment of UC. We have very little data regarding the efficiency of enteral nutrition in CD that is exclusively confined to the colon, although its remission rates might not show any differences compared to other locations of CD[83].

Apart from the intake of calories, proteins and micronutrients, enteral nutrition using liquid formulas performs other primary therapeutic functions in CD[84]. In 1973, the therapeutic effect of enteral nutrition exclusively using basic formulas (amino acids with no antigenic capacity) was described for the first time in adults with CD resistant to other therapies[85], as similar remission rates were achieved to corticosteroids[86,87]. This ability to abate CD activity in both adults[83] and children[88], extends to efficiency in maintaining remission[89-91], allowing delay in the need for surgery or reintervention[92]. Furthermore, it is a safe treatment for which no significant adverse effects have been reported.

With regard to enteral nutrition formulas, no differences were identified between the efficiency of elemental diets and non-elemental formulas[87,93], which leads to the rejection of the previously held idea that a diet lacking in antigenic capacity could restore the altered intestinal immune response. In this respect, the therapeutic effect of enteral nutrition in CD seems to be independent from the nitrogen source used[55]. On the other hand, the fat composition of the enteral diet seems to be more important in terms of its therapeutic effect on CD[94], as this fat composition could be the key factor of the diet's therapeutic action on the disease[95]. This has been suggested by various studies, but results are difficult to interpret, which means that we do not know what the ideal fat content in enteral nutrition should be for the treatment of CD. Various studies have assessed the efficiency of supplements using n-3 PUFAs in maintaining patients with CD[96,97] and UC[98] in remission, showing that they might only prove effective for maintaining CD cases in remission, although more extensive studies are required in order to unequivocally establish the utility of these therapies. In any case, these treatments are safe and no side effects have been reported.

The precise mechanism of action through which enteral nutrition operates in CD is not well known, but it has been suggested that it could act by modulating the immune system's mucosa, regulating imbalances in the bacterial flora capable of precipitating inflammation[99,100], or by modifying the luminal content, thereby altering the expression of certain genes in the epithelium with an effect on the immune system of the mucosa, as well as reducing the exposure of the intestine to antigens.

In recent years, we have increased our knowledge of the immunoregulatory function of intestinal microflora and its possible participation in the physiopathology of IBD[101,102]. Alteration of the composition and function of intestinal microbiota could lead to increased stimulation of the intestinal immune system, epithelial dysfunction and greater permeability of the mucosa, and accordingly, the correct characterization of the components of these microflora and the definition of their functions are vital in order to consider probiotic treatment for IBD[103,104]. Probiotics have shown to be as effective as mesalazine in preventing relapses in patients with UC and in the treatment of pouchitis. Efforts have also been made to identify dietary components (prebiotics) which are capable of regulating the bacterial

composition, or which have a trophic effect on the intestinal epithelium. SCFAs (butyrate, propionate and lactate) result from the fermentation of fiber by bacterial species in the colon (*Bifidobacterium*, *Eubacterium* and *Lactobacillus*), and are an important metabolic substrate for colonocytes that promote the good functioning of the mucosa[105]. The anti-inflammatory effect of butyrate has been the most studied at different levels in the physiopathology of the inflammation[51,106], and it has been successfully tested as a treatment for patients with UC[107,108].

Parenteral nutrition is of scant therapeutic interest in IBD since diverse studies have shown that intestinal rest is not beneficial to control the disease[109,110]. Consequently, parenteral nutrition is not useful for the induction or maintenance of remission in CD, nor do we have any evidence to support its use in UC. It is also very expensive and poses an additional risk due to the use of venous catheters[111]. Its utility is therefore restricted to certain cases involving efforts to close enterocutaneous or other complicated fistulas in patients with fistulizing CD[112,113], the treatment of short bowel syndrome following extensive resections for CD, or when enteral feeding is impractical for other reasons.

PRACTICAL CONSIDERATIONS

IBD is an important risk for malnutrition. Nutritional support using liquid formulas should be considered as a primary treatment for all patients with CD and in serious cases of UC, but especially for children and for those who may require prolonged cycles of corticosteroids, such as the youngest patients, those who are corticodependent, or those who present other risk factors for osteoporosis. Enteral nutrition may be considered both as a primary treatment and as a supplement to other medication in order to achieve or maintain CD remission[91].

A rich and varied diet should be recommended for all patients with IBD during remission, which includes fruit and vegetables, meat, olive oil and fish, especially blue fish. There are no reasons to restrict insoluble fiber in the diet except in the case of significant intestinal stenosis or when irritable bowel syndrome might co-exist that does not respond to other therapies. We do not have any studies that support the restriction of fiber in the diet during flares of the disease but the consumption thereof could be temporarily restricted at this time.

Because of their calcium content, dairy products are especially recommended for these patients and milk should only be restricted in the case of lactose intolerance, substituted by other fermented products (yoghurts and cheese) or calcium-enriched soya-based products. Calcium and vitamin D3 supplements are also required during treatments with systemic steroids and with those with a greater local effect, such as budesonide or beclomethasone. Iron and folic acid deficiencies should be routinely monitored in patients with IBD due to their high occurrence. Deficiency in one or both micronutrients is the main cause of anemia in these patients and can be easily remedied. We should warn that ferritin is an acute phase reactant that increases during inflammation, which restricts its value as a marker of ferropenia in IBD. For treating iron deficiency in IBD, iron can be orally or intravenously administered; the latter is recommended in cases of active inflammation in CD, since oral supplementation might be of limited efficacy. The absorption deficiency of vitamin B12 contributes to anemia and hypercoagulability. The resection or involvement of the terminal ileum in CD requires vitamin B12 supplementation *via* the parental route.

Ileum actively participates in enterohepatic circulation, which refers to circulation of bile acids from the liver where they are produced, to the small intestine, where they aid in digestion of fats and other substances, back to the liver. In this way, the distal ileum is necessary for fat and fat-soluble vitamin absorption. CD patients frequently undergo resection of the terminal ileum, and if a large segment of bowel is removed, malabsorption of these lipid diet components may appear.

The prevention of therapeutic non-compliance in IBD also includes nutritional supplements to diet and medication. In complying with nutritional treatment, aspects such as flavor, presentation, tolerability to the food, its potential adverse effects (diarrhea, nausea), the patients' motivation and that of the healthcare professionals who attend them, are influential. Attention should be paid to the distribution of the doses during the day and to the simultaneous administration of other solid food, together with the preferences of the patients themselves[55].

A number of commercial supplements are available that provide nutritional support in IBD, are wide in variety in terms of composition and nutritional content, and have a diversity of flavors allowing personal choice. We must warn that, for palatability reasons, the elemental or semi-elemental formulas are more suitable for administration *via* a nasogastric tube. Feeding using a nasogastric tube may also be considered for patients with specific protein or energy intake requirements, which for different reasons, can not be satisfied by oral means, but they may be fed a nutritional supplement *via* a tube during the night.

As detailed above, guaranteeing a sufficient calorie and protein intake can be a complicated task that may require the involvement of nutritionists and dieticians. Mutual trust between the patients, their families and the health professionals is vital to ensure the sufficient level of motivation for the adequate long-term nutritional compliance required by a chronic disease. Enteral nutrition is considered the number one treatment for CD in children, as an alternative to immunomodulatory drugs, due to its excellent safety record and advantages concerning growth. In these cases, cooperation between the patient's family and the professionals who care for him or her are particularly important to guarantee correct nutritional support.

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