
INFLAMMATORY BOWEL DISEASES. PRINCIPLES OF NUTRITIONAL THERAPY

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Inflammatory Bowel Diseases - ulcerative colitis and Crohn's disease- are chronic gastrointestinal inflammatory diseases of unknown etiology. Decreased oral intake, malabsorption, accelerated nutrient losses, increased requirements, and drug-nutrient interactions cause nutritional and functional deficiencies that require proper correction by nutritional therapy. The goals of the different forms of nutritional therapy are to correct nutritional disturbances and to modulate inflammatory response, thus influencing disease activity. Total parenteral nutrition has been used to correct and to prevent nutritional disturbances and to promote bowel rest during active disease, mainly in cases of digestive fistulae with high output. Its use should be reserved for patients who cannot tolerate enteral nutrition. Enteral nutrition is effective in inducing clinical remission in adults and promoting growth in children. Due to its low complication rate and lower costs, enteral nutrition should be preferred over total parenteral nutrition whenever possible. Both present equal effectiveness in primary therapy for remission of active Crohn's disease. Nutritional intervention may improve outcome in certain individuals; however, because of the costs and complications of such therapy, careful selection is warranted, especially in patients presumed to need total parenteral nutrition. Recent research has focused on the use of nutrients as primary treatment agents. Immunonutrition is an important therapeutic alternative in the management of inflammatory bowel diseases, modulating the inflammation and changing the eicosanoid synthesis profile. However, beneficial reported effects have yet to be translated into the clinical practice. The real efficacy of these and other nutrients (glutamine, short-chain fatty acids, antioxidants) still need further evaluation through prospective and randomized trials.

DESCRIPTORS: Inflammatory bowel disease. Nutritional therapy. Total parenteral nutrition. Enteral nutrition.

Inflammatory Bowel Diseases (IBD) are often associated with significant nutritional disturbances, such as protein-calorie malnutrition and vitamin and trace element deficits. Such problems are aggravated by complications that occur during the evolution of the disease, like bowel obstruction, need for intestinal resections and disease activity^{16, 19}. Thus, appropriate nutritional management of IBD patients is an essential part of their management.

When analyzing nutrition and IBD, three major aspects must be concerned: the influence of nutritional compo-

nents in its pathogenesis, the impact of IBD on nutritional status and the potential role of nutritional therapy (NT). Although important advances have been recently achieved in the understanding of IBD pathogenesis, there is still no consensus regarding the indications and standards of NT for these patients^{6, 26, 79}.

This article reviews the importance of nutritional deficits and their mecha-

nisms in IBD, discussing the role and efficacy of enteral and parenteral nutritional therapies.

Etiology and pathogenesis of IBD

IBD are characterized by chronic and recurrent inflammation of the bowel wall due to interaction of genetic, environmental and immunologic factors^{32, 72}.

Initially one accepts that an unspecific event (probably infection) triggers a deregulated inflammatory and immune response in a genetically susceptible individual. In a second stage

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this response is amplified through the involvement of macrophages, lymphocytes and neutrophils¹⁷. Whether this initial activation of immunologic effectors is triggered by an intrinsic (primarily deregulated immune system) or extrinsic factor (an abnormal breakdown in mucous barrier) is still unknown⁵². Mucous barrier breakdown and the continuous exposure to lumen dietary or bacterial antigens perpetuate the inflammatory cascade. Chronic inflammation results, then, from the interaction between the antigenic stimuli and individual genetic and immunologic factors.

Polymorphonuclear cells, monocytes and macrophages represent the first line of intestinal defense. When activated, phagocytes present antigens to T cells, promoting the synthesis of numerous mediators like cytokines, arachidonic acid metabolites (eicosanoids), platelet activating factor, bioactive amines, proteases, neuropeptides, nitric oxide and oxygen free radicals⁷².

The amplification of inflammatory response is more important in the pathophysiology of intestinal tissue lesions and histological alterations in IBD than the initial event itself. Moreover, effective therapeutic drugs act by modulating the production of inflammatory mediators; thus, even though the initial event remains unknown, it is believed that therapeutic advances may occur by pharmacological modulation of inflammatory mediators.

Beside genetic factors, geographic variations in the incidence of IBD and the increasing incidence of Crohn's Disease (CD) in the last decades suggest that some environmental factors might influence their pathogenesis. Among those, dietary intake of sugars, fibers, fruits, vegetables, fats and proteins have been studied²⁶. Even though some potentially important correlations have been found, the role of these

nutrients in IBD still needs more conclusive evidence¹⁶.

Nutritional deficits. Incidence, causes and consequences

IBD symptoms include increased bowel movements, blood loss, abdominal pain, nausea, vomiting and anorexia. Due to these alterations, prevalence of IBD associated-malnutrition is high, ranging from 23% in outpatients to 85% in patients admitted for clinical exacerbation^{25, 39}. Malnutrition is influenced by disease activity, length and site of inflammation. Nutritional deficits are more common in small bowel CD than when inflammation is confined to the colon⁵⁴.

Adequate nutritional care for IBD patients requires identification and correction of malnutrition-associated factors, represented by either local and systemic alterations or drug side effects (Table 1).

The reduction of dietary intake is the main cause of malnutrition. It results from the fear of provoking abdominal pain or diarrhea and imposed

dietary restrictions (“therapeutic fasting”) during activity phases. Acute anorexia is related to increased levels of the cytokines IL-1 and TNF³⁵.

Obstruction, fistulas or extensive bowel inflammation also contribute to decrease dietary intake, absorption and body protein mass. Resection of the terminal ileum can cause bile salt and B12 deficiencies, leading to malabsorption of fats and fat-soluble vitamins. Bacterial overgrowth due to fistulas, blind loop syndrome and bowel stenosis might also impair nutrient absorption. Exsudative protein loss occurs in areas of inflammation and mucosa ulceration, being proportional to disease activity.

Some nutritional deficits can also be caused or amplified by the use of drugs, such as corticosteroids (calcium), sulfasalazine (folates), and cholestiramine (vitamins). Sulfasalazine, 5-amino salicylic acid and metronidazole can cause nausea, vomiting, taste derangement and dyspepsia.

Other nutritional deficits occur in variable incidences, such as anemia (54 to 80%), hypoalbuminemia (25 to

Table 1 - Factors involved in the development of malnutrition in Inflammatory Bowel Diseases.

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- *Inadequate oral intake*
abdominal pain, diarrhea, anorexia, nausea, vomiting, alimentary restrictions, side effects of medications
 - *Malabsorption*
extensive intestinal disease, surgical resections, biliary salt deficiency, bacterial overgrowth, digestive fistulas, side effects of medications
 - *Increased intestinal loss*
bleeding, digestive fistulas, protein- and biliary salt-losing enteropathy, loss of electrolytes and minerals
 - *Increased calorie needs*
growth period, acute inflammation, sepsis, fistulas, fever, disease activity
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Table 2 - Factors determining tissue damage in Inflammatory Bowel Diseases.

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- Reduction in splanchnic flow;
 - Damage mediated by cytokines and oxygen free radicals;
 - Lower availability of antioxidant nutrients (glutamine, glutathione, zinc, selenium, vitamins A, C and E);
 - Absence of enteral nutrition and/or insufficient supply of enterotrophic nutrients (glutamine, short-chain fatty acids);
 - Diminished cellular capacity of using trophic nutrients or cellular resistance to growth hormone (GH) action.
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80%), metals (iron, copper), trace elements (selenium, magnesium, zinc), vitamins (A, B, D, E, K) and reduction of enzymatic (superoxyde dismutase, catalase, glutathione peroxydase) and non-enzymatic anti-oxidant activity (vitamins C, E, b-carotene, glutathione, taurine).

Anemia, a very frequent finding, may be due to iron, folates and cobalamine (B12) deficiencies, chronic inflammation, intestinal resections, or stool blood loss.

Hypoalbuminemia results from anorexia, lower protein intake, reduced hepatic synthesis, intestinal loss and catabolism (inflammation, fever or corticosteroid administration). Greater losses are due to disease activity rather than its location¹⁶. Therefore, serum albumin levels are considered a better marker for disease activity than nutritional status, which can be better analyzed through serum protein-binding retinol and pre-albumin²⁶. Other significant changes in body composition are related to disease activity, like fat and water losses^{11, 49}.

Nutritional deficits are associated with adverse clinical outcome, affecting cellular and humoral immunity, linear body growth and sexual maturation in children, fistula and wound healing, nitrogen balance and bone decalcification. Moreover, reduced blood loss tolerance, greater postoperative morbidity rates and slower functional recovery can occur³².

An interesting study by Schneeweiss et al.⁷³ showed that active CD patients manifest alterations in substrate oxidation similar to those observed during prolonged fasting (lower oxidation of proteins and glucose and higher metabolism of fats), without changes in energy requirements. These data demonstrate that weight loss in these patients results from anorexia, malabsorption and intestinal losses, rather than hypermetabolism. As reintroduction of normal

dietary intake can reverse metabolic changes, the importance of NT in this population is well recognized.

There are differences in the development and progression of nutritional deficits in ulcerative colitis (UC) and CD. Patients with CD develop malnutrition slowly, with frequent severe deficiencies. On the other hand, patients with UC usually preserve nutritional status, but can develop severe deficiencies very fast due to disease activity.

Thus, the most appropriate management of IBD requires attention to nutritional aspects from the initial diagnosis and the institution of necessary therapeutic measures. For this purpose, data from nutritional inquiry, physical examination, anthropometrical measures and biochemical analyses are taken into account together⁸⁷. However, difficulties in staging nutritional deficiencies in chronic disease do exist, because it is usually difficult to differentiate nutritional changes due to disease or related to malnutrition³.

NUTRITIONAL THERAPY IN IBD

General Measures

There does not exist a single uniformly effective dietary protocol for patients with IBD³. The majority of outpatients can usually adopt liberal dietary intake of calories and proteins, enough to keep and/or restore body mass and to promote adequate development of children and adolescents. Even though many patients avoid a series of foods for many reasons, they should be encouraged to use almost normal diets, provided that some restrictions might be necessary based on individual intolerance³².

Thus, patients with lactose intolerance benefit from its restriction, lowering intestinal gas production and diarrhea. Patients with intestinal steno-

sis must avoid food rich in fibers, such as corn grains, seeds, fruits and vegetables. Patients with active ileal disease or previously resected must adopt low fat diets. The substitution of common fat by medium chain tryglycerides is necessary in the presence of steatorrhea. Some patients must also restrict oxalate ingestion to prevent urinary stone formation. Attention must be given to the detection of some micronutrient deficiencies, such as iron, calcium and cobalamine.

Most patients manifest iron-deficiency hypochromic microcytic anemia, treated with iron supplements. Iron serum levels should guide provision of supplementary vitamin B12. Refractory anemia can be managed with oral iron and recombinant subcutaneous erythropoietin for 12 weeks⁷⁵.

CD symptomatic patients should receive multivitamin and mineral supplements. Zinc deficiency due to prolonged diarrhea can be corrected with a daily dosage of 20-50 mg. Risk of osteoporosis (corticotherapy, postmenopausal women, prolonged immobilization, smokers, and positive family history) is balanced with daily calcium (1,000 mg) and vitamin D (400-800 units)³.

Oral, enteral and parenteral nutritional therapy might be necessary during the different phases of IBD. When calorie and protein intakes do not match the needs for maintaining body mass in adults and adequate growth in children, some more effective nutritional intervention must be tried, such as the administration of liquid oral supplements. When the risk of malnutrition persists, the benefits and risks of enteral or parenteral nutrition must be considered.

Currently, there is no solid evidence to support caloric supplementation over the metabolic need predicted by the Harris-Benedict formula; however, patients with less than 90% of ideal body mass might need more calo-

ries, mainly during active disease³⁹. On the other hand, protein needs are usually higher in IBD patients. Therefore, adequate estimates of caloric (25-35 kcal/kg/day for adults), protein (1.0-1.5 g/kg/day for adults; 2.0 g/kg/day for malnourished or septic patients), water and electrolyte needs are essential and require attention to individual needs¹³.

Endpoints, indications and selection of route

The merits of anti-inflammatory drugs in the treatment of IBD are well established^{82, 83}. Drugs such as prednisone, azathioprine, sulfasalazine and mesalamine have achieved therapeutic response levels around 60 to 80%, *versus* 30% with placebo⁴⁷.

However, side effects with significant impact on the patient's quality of life keeps alive the search for alternative therapeutic measures to control malnutrition and inflammation. Thus, the efficacy of NT must be analyzed with those results in mind.

The main goals of NT are the maintenance and / or recovery of nutritional status, remission of disease activity, reduction of surgical indications and postoperative complications⁶. Decisions regarding the appropriate use of NT require an integrated evaluation of patient's nutritional status, severity of disease, digestive tract function and need for surgical treatment.

Generally, the enteral route is preferred since it is associated with fewer complications and lower costs, thus saving the parenteral route for patients with contra-indications or intolerance for enteral feeding. These cases include massive hemorrhage, intestinal perforation or obstruction, toxic megacolon, and some cases of extreme short bowel syndrome.

Specialized NT is indicated in acute, severe and recurrent exacerbation, preoperative preparation of mal-

nourished patients, digestive tract fistulas, short bowel syndrome (anatomic or functional), and growth retard. Usually, many of those indications are based on clinical expertise rather than on clinical trials results. The rationale of these indications lies on the fact that malnourished patients have wound healing and immunologic impairment. Reviews of uncontrolled studies in malnourished patients reveal that preoperative total parenteral nutrition (TPN) reduces complications and the extent of intestinal resection, even though increasing hospital admission lengths³.

With these data in mind, severity of disease and the period of inadequate nutritional intake have been often used as criteria for NT indication, rather than diagnosis of IBD itself. During a 5-7 days period of inadequate nutritional intake, well-nourished patients have only moderate metabolic stress with minimal functional consequences. However, greater metabolic stress or malnutrition shorten this period and force earlier institution of NT⁴⁹.

IBD during childhood or early adolescence has a great impact on nutritional status and growth. The prevalence of linear growth retard in large series varies from 36 to 88%³³. In these patients, NT is indicated as an adjunct to correct and to prevent malnutrition, promoting growth and as primary therapy for active inflammation, especially in CD²¹.

Growth retard has multifactorial etiology, and it is mainly related to inadequate food ingestion and anorectic effects due to increased expression of cytokines (TNF- α). Serum changes in growth hormone levels have also been implicated^{33,35}.

The response to enteral nutrition (EN) in children is similar to that observed in adults, and male patients are more vulnerable to growth impairment since it occurs in a later period. In pediatric patients, night time infusion

of dietary solutions is a common practice, avoiding major interference with everyday activities³².

The use of EN in children must take into account their acceptance and tolerance as many products have unpleasant tastes and are delivered through nasogastric feeding tubes. This problem is partially controlled by using polymeric rather than elemental diets, without reduction in treatment efficacy.

The benefits of bowel rest, TPN and elemental diets in patients with refractory CD have been known for more than 25 years, including better nutritional status, symptomatic relief and even temporarily complete clinical remission¹⁶. The use of NT for controlling symptoms and signs of a disease is called *primary nutritional therapy*.

Both CD and UC exhibit different responses to enteral and parenteral nutritional support. Recently, excellent literature reviews^{50,66,81} and meta-analyses^{22,34} concerning primary NT of IBD have been published.

Total Parenteral Nutrition (TPN)

TPN aims are preoperative bowel rest, fulfilling postoperative nutritional requirements and correcting malnutrition. It can also be used as primary therapy for active and severe IBD³⁹. Bowel rest is believed to improve control of intestinal inflammation reducing the presence of antigens and bacterial growth in the lumen, reducing peristaltic movements and digestive tract secretion, leading to relief of symptoms⁷⁷.

In other cases, TPN can be used as a complement to poorly tolerated or quantitatively insufficient oral or enteral nutrition to maintain patient's nutritional status or to correct malnutrition⁶⁰.

Indication of primary TPN and bowel rest for acute active IBD is still controversial, since total bowel rest is not essential for disease remission³¹.

Furthermore, it is well known that exclusive TPN leads to profound morpho-functional changes (mucosal atrophy, bacterial translocation, enzyme and hormone alterations, intrahepatic cholestase, and macrophage dysfunction). For that reason, it has gradually lost space in face of the benefits associated to nutrient provision directly to the mucosa¹⁸. Moreover, the use of TPN adds significant costs and length to hospital admissions, especially when septic, metabolic or venous access complications occur²⁰.

Malnutrition related complications occur in a significant number of IBD patients after surgical treatment³⁸. Reduction of these complications with at least 5 days of preoperative TPN is well observed in patients with severe malnutrition, presenting low serum albumin (< 3.5 g/dL) and transferrin (< 150 mg/dL) levels⁷⁰. In these situation, TPN provides nutritional requirements, preserves lean body mass and functional capacity and prevents protein loss in acute disease course^{4,11}.

In primary NT the association of bowel rest and TPN reduces mucosal inflammation and disease activity. During acute toxic colitis, TPN maintains protein reserves, provides calories and reduces surgical complications¹⁵. However, the likelihood of total remission with TPN decreases with more severe acute disease course, even when it is associated with optimal clinical treatment⁵⁹. TPN also shows fewer benefits during acute courses of UC than CD⁷⁷.

Classical indications of TPN in CD patients are remission of acute disease, control of abdominal pain and subocclusive episodes⁷⁶. Therefore, TPN has a potential primary therapeutic role in acute CD, with favorable clinical response in cases of ileitis^{19,77}. In cases of intestinal obstruction, TPN is essential in malnourished patients and when one previews a fasting period greater than 5 days.

TPN can become a valuable alternative for obtaining symptom remission and postponing surgical indications, especially in refractory corticoid therapy⁵³. However, even though TPN is effective in refractory CD with an average hospital remission of 64% (40 to 80%) in the short term, reviews on the subject showed less encouraging long term remission (less than 50%)^{16,39,79}.

The observed numeric variations occur due to different populations, length of TPN, definitions for remission and recurrence and simultaneous use of medications. Han et al.³⁹ prospectively analysed 170 patients with CD, showing an 81% initial clinical remission that was reduced to 23% after 12 to 24-month follow-up. Fisher²³ reported greater remission rate (75%) in patients with small bowel than in those with colonic CD (50%). However, this better response was not uniformly observed in other series^{59,76}.

In a series of 100 patients with refractory CD with optimal clinical treatment, the addition of TPN was effective for clinical remission in 75%, relieved obstructive symptoms in 75%, decreased the inflammatory mass in 82% and achieved fistula healing in 62%⁶⁵. Significant reduction in disease activity index, weight gain and elevation of serum albumin levels were also achieved in these patients.

Fistulas due to CD are common, because of the characteristic transmural inflammation. Complicated or symptomatic fistulas usually require surgical treatment. Numerous reports about the effects of TPN in intestinal fistulas reveal initial closure rates of 44%³⁹. Indeed, low output cutaneous fistulas may have some benefit from TPN, reducing morbidity and improving local conditions for surgical treatment³. However, there is still a lack of controlled prospective studies on this matter.

Other possible indication for TPN is perianal CD, which treatment is usu-

ally conservative due to frequent recurrences and possible involvement of sphincter muscles. Early NT in malnourished patients can promote bowel rest and improve local wound healing⁸³.

Long-term TPN has an important role in maintaining nutritional status and improving quality of life in short bowel syndrome or chronic subocclusive disease. Home TPN produces dramatic results in CD patients with less than 100 cm of jejunum or less than 50 cm of jejunum with intact colon, but also in cases of congenital and ischemic anomalies, motility disorders, radiation enteritis and trauma⁴⁴.

In patients with UC, TPN is not considered an effective primary treatment. Prospective and retrospective studies showed remission rates lower than 40% (initial) and 10 to 30% (late), results not different than those obtained in control groups³⁹.

The presented data indicates that TPN should be offered to IBD patients in need for NT who do not tolerate the enteral route, especially during acute and severe disease courses. The available experience supports the use of TPN for at least 5 days to correct severe preoperative malnutrition in elective surgical situations or at least 1-3 days in cases of intense disease activity⁴.

TPN is also effective as primary treatment in refractory CD, even though a higher late recurrence rate is observed when compared to surgical treatment. On the other hand, primary TPN is not effective in the treatment of complex CD fistulas and UC.

Finally, long-term home TPN plays a major role in improving the quality of life of patients with CD and severe short bowel syndrome.

Enteral Nutrition (EN)

EN comprises direct delivery of nutrients to the gastrointestinal tract

through different liquid formulas administered by naso/oral or enteral tubes, percutaneous feeding tubes or gastrostomies / jejunostomies. In IBD, EN is provided to correct nutritional deficits or serve as primary therapy for clinically active disease.

Polymeric diets are most often prescribed, mainly in patients with adequate gastrointestinal function. Elemental diets contain nutrients in its simple form, being historically indicated for patients with malabsorption. Intolerance to polymeric diets and short bowel syndrome are the main indications to semi-elemental (oligomeric) and elemental formulas.

Recently, the recognition of TPN potential complications and the benefits of direct nutrient delivery to the gastrointestinal lumen have reaffirmed the importance of EN in several conditions. Other advantages include lower costs, easy administration and lower complication rates. Even though frequent, complications like diarrhea, flatulence, colicky pain, gastroesophageal reflux and aspiration are less severe than those caused by TPN.

Despite the benefits of EN in the treatment of CD, the simplicity of drug treatment makes that the obvious choice. The palatability of enteral diets, monotony of use of liquid formulas and the frequent need for tube feeding can make EN very little attractive. On the other hand, EN does not cause side effects such as osteonecrosis, muscle mass loss and psychological disturbances, as observed with steroids.

If intestinal obstruction is not present, there is no contra-indication to EN¹⁵. Furthermore, the similar early remission rates of enteral diets and TPN in CD suggest that bowel rest provided by TPN does not influence the efficacy of treatment⁵¹.

Despite its therapeutic effects have been known for more than two decades, the use of EN still raises controversy¹⁵. The potential role of EN in the primary

treatment of active CD was discovered by chance, when patients treated with elemental diets preoperatively preserved nutritional conditions and also had inflammatory activity controlled⁸⁶.

Elemental diets were introduced initially as primary treatment for active CD due to its low allergenic capacity, providing lower antigenic (since they don't have integral proteins or peptides) and inflammatory stimulation. As absorbed by the proximal jejunum, elemental diets provide nutrients and trophic stimuli for this segment, keeping the distal small bowel and colon (more common sites of CD activity) at relative rest. Elemental and oligomeric diets also reduce the bacterial load, decreasing intestinal permeability.

Elemental and polymeric diets can induce active CD remission as effectively as corticosteroids¹⁵. However, there aren't enough data to support the substitution of drug therapy by EN⁵⁰. Beside other mechanisms, EN decreases CD activity by decreasing the synthesis of inflammatory mediators and by providing specific nutrients^{16,32}.

Comparative studies have reported that steroids and sulfasalazine therapy are superior when compared to elemental diets^{55,57}. Meta-analyses of randomized controlled trials also favor drug therapy over EN regarding remission of active CD in adults^{22,34}. Moreover, results about late remission rates reached the same conclusion²⁹, although the use of exclusion diets may improve late remission rates⁶⁸.

Comparative studies regarding the efficacy of different EN formulations in active CD have questioned the role of elemental formulas. Rigaud⁶⁷ showed similar results with elemental and polymeric diets used as primary therapy for steroid-unresponsive CD. This fact suggests that some patients may benefit from NT after drug treatment failure¹⁵. In a prospective study comparing TPN, oral diets plus TPN

and elemental diets, Greenberg et al.³¹ observed no significant differences on remission, concluding that the benefits of these regimens were due to nutritional improvement. Recent literature reviews^{22,50} and meta-analyses of controlled randomized trials³⁴ have not shown any significant difference between elemental, oligomeric and polymeric diets concerning initial or late remission of active CD, even though elemental diets are related to earlier remission.

Although differences in nitrogen sources of enteral feeds are not relevant to their therapeutic efficacy, polymeric diets should be preferentially used in treatment of acute CD, once it offers lower costs, better patient tolerance, and the possibility of immunological action of its contents⁸⁵. Furthermore, the lipidic composition of polymeric diets includes oleic acid, a mono-unsaturated fatty acid that is not a precursor of eicosanoids or arachidonic acid. This advantage is not found in regular oral diets, rich in linoleic acid.

Concerning clinical remission, drug treatment is more efficient than EN therapy; on the other hand, late remission rates are significantly higher than those observed using placebo (20 to 40%) in mild or moderate CD^{3,33}. These results suggest that EN, when tolerated by the patient, is beneficial.

The use of EN in active CD during 3 to 6 weeks may decrease disease activity and induce early remission (before 3 months) in 29 to 88% (average 68%) of patients^{16,22,30}. Further studies showed that TPN and elemental diets have similar early remission rates, whereas TPN and polymeric diets have similar effect on late remission; remission rates after one year of EN treatment varied from 0 to 56%, and from 17 to 50% for TPN¹⁹.

The use of different formulations and patient selection biases may be the cause of different success rates using EN. A negative correlation be-

tween remission rates and long-chain triglyceride intake was observed in a meta-analysis of 15 randomized controlled series⁶¹. EN efficacy is also limited by disease location, once ileal disease has a faster and more complete response to treatment when compared to more diffuse disease or colonic or perianal disease^{15,33}. Another limitation is the early relapse that occurs in 60 to 70% of patients in one year⁶⁷. Despite the benefit of early remission induction on active CD, further data are necessary for better evaluation of enteral diet therapy on CD complicated by fistula and stenosis.

In children with CD, disease activity is the most important cause of growth failure. In this group, the need to maintain remission of active disease for longer periods has brought forward two different nutritional strategies: exclusive EN therapy for 30 days plus cyclic refeeding, and daytime free diet plus night time EN supplement (nasogastric route, 4-5 times per week)³³. The use of enteral diet enriched with transforming growth factor beta 2 (TGF- β 2) has also shown benefits such as histological improvement and reduction of IL-1, IL-8 and IFN- γ production by the mucosa²¹.

Due to the undesirable side effects of steroid therapy on normal growth, EN may be more appropriate in children and teenagers, even though primary NT is not as effective as drug therapy.

In general, EN should be preferred to TPN in NT. As primary therapy to active CD, data suggest that EN has equal efficacy compared to TPN, but it is less effective compared to corticosteroids. EN plays an important role in selected cases unresponsive to usual treatment and in children / teenagers.

Although remission rates of elemental and polymeric diets are similar, it is known that polymeric diets are more efficient concerning the improve-

ment of nutritional state. The association between lower remission rates and LCT intake still needs confirmation⁴⁷.

Finally, EN is not efficient as primary therapy for clinical remission of ulcerative colitis patients^{28,59}.

SPECIFIC NUTRIENTS IN NT

In IBD, some factors may lead to intestinal epithelial cells damage, and some nutrients are important to maintain intestinal structure and function (Table 2). Treatment of gastrointestinal diseases with specific nutrients is a new therapeutic modality based on their pharmacological properties. This concept is called pharmacological nutrition.

Thus, a rational plan must include nutrients to provide calories, to induce low antigenic stimuli, to regulate inflammatory and immunologic responses and to stimulate mucosal trophism^{41,75}.

Glutamine (GLN) is the most common aminoacid in mammals' blood. It is considered the main oxidative fuel of epithelial cells, especially jejunal enterocytes⁸⁰. Although GLN is a non-essential aminoacid, experimental and clinical data suggest that it may become conditionally essential in catabolic states^{9,80}. Since conventional TPN solutions and enteral nutrition do not provide adequate amount of GLN to a catabolic patient, GLN supplementation may improve structural integrity, function and intestinal recovery in catabolic conditions associated to radiation therapy, chemotherapy, inflammation, trauma and sepsis^{7,48}.

However, the limited data concerning the use of GLN suggest that there is not clear evidence of its therapeutic role in IBD^{3,14,24,78,88}.

Short chain fatty acids (SCFA) are organic fatty acids derived from the bacterial degradation of dietary carbohydrate^{5,12}. More than 90% of the

SCFA found in humans are acetate, propionate and butyrate.

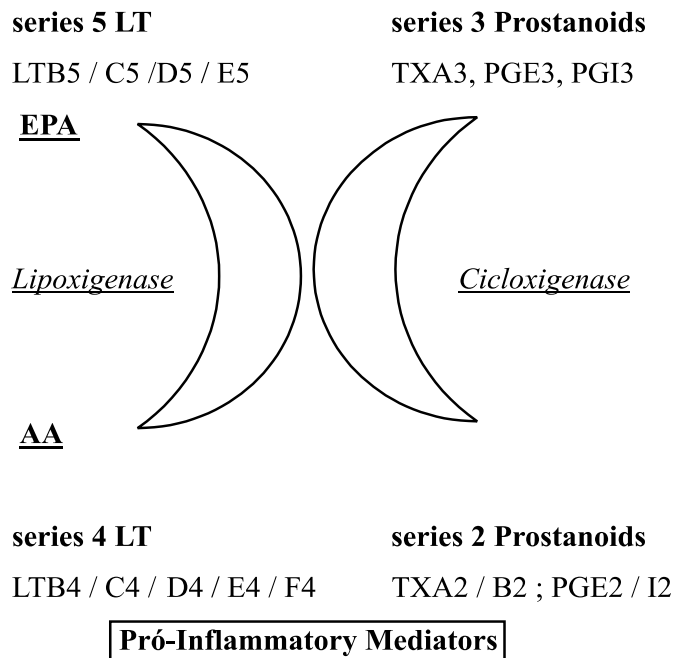
Nowadays it is a consensus that SCFA have an important role in normal colon physiology, once they are the main energy source to the colonocyte. They also stimulate cellular proliferation, visceral blood flow and enhance sodium and water absorption from the intestinal lumen. Butyrate is the main oxidative fuel of colonocytes, representing 70% of the total energy consumption^{10,43,74}.

Besides this, data concerning SCFA role in the physiopathology and management of ulcerative colitis (UC) are contradictory^{69,43,74}. The association between SCFA and "pouchitis" after restorative proctocolectomy (RPC) has also been a matter of discussion, in what the occurrence of fecal stasis could lead to important changes in luminal environment, like bacterial overgrowth, bile acids action and SCFA alterations^{5,71}.

It has also been discussed if pouchitis and UC could have a common etiology, UC recurrence being proposed as a cause of pouchitis^{64,84}. However, the association between SCFA and pouchitis deserves new controlled trials for better comprehension.

Recently, the potential role of lipid emulsions supplemented with omega-3 fatty acids (n-3 FA) has received great attention regarding nutritional therapy in several conditions^{1,62}. It is well known that exogenous provision of fish oil-derived FA promotes a fast enhancement of n-3 FA plasmatic concentrations, establishing an extracellular enzymatic competition between n-3 FA and arachidonic acid (AA), decreasing pro-inflammatory mediators synthesized from AA and increasing the concentration of less potent inflammatory mediators synthesized from n-3 FA^{1,36} (Fig. 1).

In IBD patients, treatment with oral or parenteral n-3 FA has had favourable results in clinical trials and experimen-



LT = leukotrienes; PG = prostaglandins; TX = thromboxanes

Figure 1 - Eicosanoids derived from eicosapentanoic (EPA) and arachidonic (AA) acids.

tal studies, decreasing symptoms, corticosteroid needs, and promoting colonic histological and endoscopic improvement^{2,27,40,58}. These effects are attributed to alteration in the inflammatory mediator profile⁶³.

Literature data suggest that parenteral n-3 FA leads to more effective and earlier benefits when compared to the enteral route. It is believed that fast changes in plasmatic and membrane FA composition lead to al-

terations on lipidic mediators synthesis and earlier clinical results^{8,37,46}.

Otherwise, parenteral utilization of n-3 FA still requires evaluation of other factors such as triglyceride chain dimension, treatment duration, n-3/n-6 ratio and association to other immune modulator nutrients. Further assessment of efficacy, costs, risks and side effects will bring new lights into the treatment of IBD with immune modulatory therapies⁵⁶.

CONCLUSIONS

Malnutrition in IBD patients is frequent, multifactorial and has many deleterious consequences. Its management requires identification of nutritional deficits in order to choose the best nutritional therapy in each situation.

TPN may correct nutritional deficits, maintain nutritional status and serve as primary therapy in patients with active CD. However, due to the associated high costs and complication rates, EN is the route of choice for nutritional therapy. Several studies attested the efficacy of enteral formulations to control disease activity in CD patients.

Clinical and experimental use of trophic nutrients as glutamine, SCFA, and immune modulator nutrients as n-3 FA brought up new perspectives. Despite positive preliminary results, further prospective and controlled trials are necessary to establish their role in IBD management.

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RESUMO

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CAMPOS FG e col. - Doenças inflamatórias intestinais. Princípios da terapia nutricional. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 57(4):187-198, 2002.

As doenças inflamatórias intestinais - retocolite ulcerativa inespecífica e doença de Crohn - são afecções inflamatórias gastrointestinais crônicas de causa ainda desconhecida. Caracteri-

zam-se por diarreia crônica, mal-absorção, síndrome do intestino curto, disfunção da barreira mucosa e processo inflamatório intestinal, fatores que determinam deficiências nutricionais e

funcionais que ressaltam a importância da terapia nutricional em seu tratamento. As diversas formas de terapia nutricional visam corrigir os distúrbios nutricionais e modular a resposta inflamatória, podendo, desta forma, influir na atividade da doença. A nutrição parenteral total tem sido usada para corrigir os distúrbios nutricionais e proporcionar repouso intestinal na doença ativa. Seu uso deve ser reservado a pacientes que não podem tolerar a nutrição enteral. A nutrição enteral é efetiva em induzir remissão clínica da doença em adultos e promover crescimento em crianças. Devido à baixa incidência de

complicações e menor custo, a nutrição enteral deve ser opção preferencial à nutrição parenteral total quando possível. Ambas apresentam igual efetividade na terapia primária na remissão da Doença de Crohn ativa. Embora a terapia nutricional possa melhorar a evolução de muitos pacientes, é necessária uma seleção criteriosa devido a seus custos e complicações, especialmente naqueles que requerem nutrição parenteral total. Recentes pesquisas têm se dedicado ao uso de nutrientes como agentes terapêuticos primários. A imunonutrição com ácidos graxos ômega-3 se

constitui numa importante alternativa terapêutica no manuseio das doenças inflamatórias intestinais, modulando o processo inflamatório e modificando o perfil de produção de eicosanóides. Entretanto, a real eficácia deste e outros nutrientes (glutamina, ácidos graxos de cadeia curta) ainda necessitam de novas avaliações por estudos prospectivos, controlados e randomizados.

DESCRITORES: Doenças inflamatórias intestinais. Terapia nutricional. Nutrição parenteral total. Nutrição enteral.

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