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Invited Review

Role of nutrition in the management of inflammatory bowel disease – current status –

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SUMMARY

A lot of medical literature is lately dedicated to nutrition in inflammatory bowel disease (IBD). The growing recognition of the importance of nutrition in the management of IBD is reflected by the increasing number of papers dedicated to the topic and by the evidence based guidelines. When analyzing nutrition and IBD, three major aspects must be concerned: the influence of nutritional components in the pathogenesis of IBD, the impact of IBD on nutritional status and the potential role of nutritional therapy. Many nutrients are under scrutiny for their involvement in the pathogenesis of IBD: carbohydrates, fibers, fruits, vegetables, fats, proteins. Their role is still under debate. Modern food may induce in predisposed individuals mucosal damage and increased translocation, continuous exposure to bacterial antigens and sustained immunologic stimulation. Malnutrition is frequently associated with IBD and its severity is influenced by the phase of disease activity and the length and site of inflammation. It is the result of a combination of factors: inadequate oral intake, malabsorbtion, increased intestinal loss and increased calorie need. Undernutrition should be constantly suspected; therefore frequent evaluation of the nutritional status should be made along with disease treatment and follow-up. Oral intake should be adapted to individual needs and tolerance. If nutritional support is decided, enteral nutrition is the first choice. It should be adapted to the actual needs and tolerance of the patient. Enteral nutrition is the first line therapy in children with IBD. In adult patients corticosteroids are more active, but enteral nutrition should be used as adjunctive therapy. A lot of medical literature is lately dedicated to nutrition in inflammatory bowel disease (IBD). The growing recognition of the importance of nutrition in the management of IBD is reflected by the increasing number of papers dedicated to the topic: clinical trials and review papers. All these data were collected and analyzed and panels of experts formulated evidence based guidelines. The latest in the field are *The Guidelines of the British Society of Gastroenterology*, published in Gut 2004,[1] *The Guidelines of European Society of Enteral and Parenteral Nutrition, published in Clinical Nutrition in 2006*[2] and *The European evidence based consensus on the diagnosis and management of Crohn's disease*, emitted by the European Crohn's and Colitis Organization, published in 2006.[3] Currently IBD includes Crohn's disease and ulcerative colitis. Some authors add puchitis, a new disease, in which diagnostic criteria have only recently been proposed.[1] When analyzing nutrition and IBD, three major aspects must be concerned: the influence of nutritional components in the pathogenesis of IBD, the impact of IBD on nutritional status and the potential role of nutritional therapy. Currently the appropriate nutritional management of IBD is an essential part of the therapeutic surgery.

Key words: inflammatory bowel disease, nutrition, Crohn's disease, ulcerative colitis, undernutrition

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NUTRITION AND PATHOPHYSIOLOGY OF IBD

IBD is characterized by chronic and recurrent inflammation of the bowel wall due to interaction of genetic, environmental and immunologic factors.[1,4] Initially the triggering event (probably infection) results in a disregulated inflammatory and immune response in genetically susceptible persons. The second stage, the amplification of the immune response, is more important in the pathophysiology of IBD and involves macrophages, lymphocytes and neutrophils.[5] The perpetuation of the inflammatory cas-

cade is the result of mucous breakdown and continuous exposure to lumen dietary or bacterial antigens.[5]

Many nutrients are under scrutiny for their involvement in the pathogenesis of IBD: carbohydrates, fibers, fruits, vegetables, fats, proteins. Their role is still under debate. Modern food (such as gluten-containing grain) may induce mucosal damage and increased translocation in predisposed individuals,[6] continuous exposure to bacterial antigens and sustained immunologic stimulation.

The interrelation between nutrition and IBD are complex. Nutrients act at different stages of IBD pathogenesis. The intestinal ecosystem plays a pivotal role in the pathogenesis of IBD, triggering the uncontrolled inflammatory response in genetically predisposed individuals.[7] As components of cell membrane, nutrients can mediate the expression of proteins involved in the immune response (cytokines, adhesion molecules, nitric oxide synthase, a.o.).[7,8] Suboptimal levels of micronutrients are often found in patients with IBD and they may favor the self-perpetuation of the disease and cause defective defense against damage produced by oxygen free radicals and facilitate lipid peroxidation. The correlation between diet and disease activity was studied according to a dietary analysis method,[9] leading to evidence-based diet recommendations.

On the other hand food modulates the immune function, either the innate immunity (phagocytic activity, NK cells activity) or the acquired immunity (T cell response, antibody production),[10] thereby normalizing the physical status of allergic or cancer patients, or decreasing the risk of disease.

UNDERNUTRITION AND IBD

Prevalence of IBD associated – malnutrition is high. 23% of out-patients with IBD are malnourished. Patients admitted to hospital for clinical exacerbation have an incidence of undernutrition as high as 85%.

Malnutrition is influenced by the phase of disease activity and the length and site of inflammation. It is the result of a combination of factors: inadequate oral intake, malabsorption, increased intestinal loss and increased calorie need[5] (table 1). In the active phase the nutritional status rapidly deteriorates due to anorexia or fear of eating, post-prandial symptom exacerbation, increased energy consumption and exudative enteropathy (protein-loosing enteropathy).[11] Accelerated protein turnover and increased metabolism lead to decreased lean body mass and decreased internal organ proteins.[11]

Consequences of undernutrition are complex: adverse clinical outcome, impaired cellular and humoral immunity, altered growth in children, impaired fistula and wound healing, increased postoperative morbidity, slower functional postoperative recovery and ultimately decreased quality of life.

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

Nutritional deficiencies are constantly present in IBD, but their type and incidence varies with the type of disease. For instance: Hypoalbuminemia and vitamin deficits are more frequent in Crohn's disease, but anemia and hyposideremia are more frequent in ulcerative colitis[5,12] (table 2).

NUTRITIONAL THERAPY

Goals of nutritional therapy in IBD are maintenance or recovery of nutritional status, remission of disease activity, reduction of surgical indications and reduction of postoperative complications.[5] It is demonstrated that enteral nutrition in patients with acute Crohn's disease may alleviate inflammation and promote remission. Therefore the term nutritional support is replaced by the term nutritional therapy, taking into account the active therapeutic role of nutrition in influencing the pathophysiological evolution of the disease.

Table 1. Factors involved in the development of malnutrition in IBD[5]

Mechanisms	Factors
inadequate oral intake	abdominal pain, diarrhea, anorexia, nausea, vomiting, alimentary restrictions, drug side effects
malabsorption	extensive intestinal disease, surgical resection, biliary salt deficiency, bacterial overgrowth, digestive fistulas, drug side effects
increased intestinal loss	bleeding, digestive fistulas, protein-/biliary salt loosing entheropathy, loss of electrolytes and minerals
increased calorie needs	growth period, acute inflammation, sepsis, fistulas, fever, disease activity

Table 2. Incidence of nutritional deficits in IBD[12]

Deficits	Crohn's disease (%)	Ulcerative colitis (%)
Weight loss	65-75	18-62
Hypoalbuminemia	25-80	25-50
Anemia	25-85	66
Hyposideremia	39	81
Vitamin B12 deficit	48	5
Folate deficit	67	30-40
Calcium deficit	13	
Magnesium deficit	14-33	NA
Liposoluble vitamins deficit	11-75	A-35
Zinc deficit	50	NA

NA=not available

The use of nutritional therapy for controlling symptoms and signs of a disease is called *primary nutritional therapy*.[5]

The enteral nutrition is the option of choice for nutrition administration. It involves less complications and less costs. Parenteral nutrition is considered only when intolerance or contraindications for enteral feeding are present: massive hemorrhage, intestinal perforation or obstruction, extreme short bowel syndrome.

Indications of enteral nutrition are: prevention or treatment of undernutrition, improvement of growth and development in children and adolescents, acute-phase therapy (the so called primary nutritional therapy indicated in active disease), perioperative nutrition and maintenance of remission in chronic active disease.[2-4,13]

According to the temporal evolution of the disease:

- In active disease enteral nutrition may be used as sole therapy only when corticosteroids are not feasible – patient refusal or corticosteroids contraindication1-3 (grade A recommendation). Usually in the active phase of the disease enteral nutrition is used as adjunct therapy (in combination with drugs) in case of malnutrition or in case of intestinal inflammatory stenosis (grade C recommendation).1,2,5 In children with CD enteral nutrition is first line therapy in order to avoid growth and development alterations (grade C recommendation).1,2,5,13,14
- For maintenance of long lasting (>1 year) remission and in the absence of undernutrition, enteral nutrition (either as tube feeding or as oral nutrition supplements) is not indicated[2,15] (grade C recommendation).

  Oral nutrition supplements are indicated only in case of persistent intestinal inflammation, for instance steroid-dependent patients[2,15,16] (grade B recommendation).
- Perioperative nutrition is indicated to treat or prevent undernutrition, to decrease the risk of postoperative complications and to improve functional recovery. Thus, indications for perioperative nutrition are weight loss or low albumin level (grade C recommendation).[1,2]

Enteral nutritional therapy in Crohn's disease offers some advantages over drug therapy, the most important one being fewer side effects in comparison with corticosteroids. Steroid treatment is associated with severe complications (osteoporosis, muscle mass loss, psychological disturbances, abnormal growth, s.o.), which may mandate for interruption of treatment. In this case nutritional therapy offers an advantageous alternative.

The are also disadvantages of enteral nutrition: low palatability of most formulae, monotony of using liquid formulae, frecquent need for tube feeding and more complicated administration in comparison with the simplicity of drug administration.[11,14]

Enteral nutrition is applied as tube feeding or oral nutritional supplements ("sip drinks"). Both may be combined with normal food to improve nutritional status of the patient (grade A recommendation).[2] Oral nutritional supplement should bring about 600kcal/day.[2] If nasogastric, nasojejunal, gastrostomy or jejunostomy feeding is indicated, continuous administration is preferred, rather than bolus administration (grade B recommendation).[2]

Different types of enteral nutrition formulae are available. Trials showed no difference in the effect of elemental formulae (based on amino-acids), olygomeric formulae (based on peptides) or polymeric formulae (based on whole proteins)[2,3,5,16] (grade A recommendations). Therefore, nowadays aminoacids and peptide based formulas are not recommended.[2,5] The usefulness of modified enteral formulae is under scrutiny. Large trials failed to demonstrate clear benefits. Therefore there are not recommended in case of Crohn's disease (grade A recommendation).[5] There are some differences between western countries and Japan regarding indications for and evaluation of enteral nutrition in CD. Enteral nutrition with elemental diet is first line therapy for active disease leading to remission in 80% of patients,[17] probably due to removal of food antigens and decreases of secretion and motility.

Total parenteral nutrition (TPN) in CD is the exception, and not the rule. Goals of TPN in Crohn's disease are preoperative bowel rest, achievement of postoperative nu-

tritional requirements, correction of undernutrition, complement to poorly tolerated or quantitatively insufficient oral/enteral nutrition. Indications of TPN in CD are remission of acute phase and control of abdominal pain and subocclusive episodes, fasting period >5 days in malnourished patients, symptom remission and postponing of surgical indication, especially in corticoid-resistant CD and CD complicated with fistulas, short bowel syndrome or chronic suboclusive disease.[5]

In contrast to CD, there is no evidence that nutritional support alters the inflammatory response in UC.[1,2,5] Indications of enteral nutrition in UC are treatment or prevention of undernutrition in patients with inadequate oral intake.[1,2] Specific deficiencies must be treated with supplements (e.g. iron). In acute-phase or maintenance of remission there is no place for enteral nutrition in case of ulcerative colitis (grade C recommendation).[2] Some studies whow that probiotics may be effective in remission maintenance of ulcerative colitis.[18-20]

Goals of total parenteral nutrition in ulcerative colitis are preoperative bowel rest, achievement of postoperative nutritional requirements, correction of undernutrition and toxic megacolon.[1,2,20]

Generally speaking total parenteral nutrition has a lot of disadvantages: epithelial atrophy, bacterial translocation, enzyme and hormone alterations in the digestive tract, intrahepatic colestase, macrophage dysfunction, water, electrolyte and metabolic complications, a.o.[5] Therefore, in order to avoid total bowel rest when the caloric needs cannot be met by the enteral route, total parenteral nutrition should be used in combination with minimal enteral nutrition. This means the administration of small amount of enteral feeding with the goal of delivering nutrients in the digestive lumen for the nutrition of enterocytes.

Pharmacological nutrition is the administration of nutrients aiming to decrease inflammation by controlling mediators synthesis and target organ response to these mediators – the so called *immunonutrition*. The present status of clinical utilization of specific nutrients is under debate. Glutamine, short chain fatty acids and omega-3 fatty acids are under investigation in IBD, but there is a lack of concludent data.[2,21] Hence, they cannot be yet recommended as part of nutritional therapy.

Glutamine is a conditionally essential amino acid in catabolic conditions and is the principal energy source for enterocytes. Inflammation impaires glutamine metabolism and decreases availability for enterocytes. Glutamine supplementation reduces intestinal damage, improves nitrogen balance and may improve the course of IBD. But studies using glutamine supplementation of total parenteral nutrition failed to demonstrate an obvious clinical benefit.[22] On the other hand after glutamine supplementation two effects may arise: mucosal regeneration in the ileum, but exaggerated tissue injury in the colon.[23] A 2006 published paper[23] demonstrates that the net result of glutamine supplementation is beneficial in the treatment of inflammatory small-bowel disease, but may be deleterious in colitis.

The composition of fat in the nutritional preparation may influence the synthesis of inflammatory mediators.[7,24] The increased amount of omega-3 polyunsaturated fatty acids (as in the fish oil) may result in modulation of inflammatory response.[3,5,25-28] Immunonutrition is under scrutiny in several conditions associated with inflammation and dysregulated immune response. A double blind randomized multicentre European trial demonstrated better remission rates in case of enteral nutrition with fish oil-rich formula in comparison with standard formula.

In conclusion all patients with IBD benefit from nutritional management. Undernutrition should be constantly suspected, therefore frequent evaluation of the nutritional status should be made along with disease treatment and follow-up. Attention should be paid to micronutrients deficiencies, which should be early diagnosed and treated. Oral intake should be adapted to individual needs and tolerance. Oral nutritional supplements should be used on individual basis.

If implementation of artificial nutrition is decided, the enteral route is preferred. Enteral nutrition should be adapted to the actual needs and tolerance of the patient. There are no differences between the effects of elemental and polymeric formulae, therefore polymeric enteral preparations are preferred.

Enteral nutrition is the first line therapy in children with IBD. In adult patients corticosteroids are more active, but enteral nutrition should be used as adjunctive therapy.

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