Progress in Nutrition 2015; Vol. 17, N. 2: 79-86

Review

Nutrition in IBD patient's: what are the prospects?

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«Aspetti nutrizionali nei pazienti affetti da IBD: quali prospettive?»

Summary. Inflammatory bowel disease (IBD) is a chronic disorder characterized by a relapsing-remitting course, which alternates between active and quiescent states, ultimately impairing a patients' quality of life. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). In physiological conditions the gut is costantly exposed to various antigens, commensal microflora and pathogens and the inflammatory response is finely balanced. It is thought that a vast number of environmental risk factors may be implicated in the development of IBD, including smoking, dietary factors, psychological stress, use of non-steroidal anti-inflammatory drugs and oral contraceptives, appendectomy, breastfeeding, as well as infections. Nutritional support, as a primary therapy, has a crucial role in the management of patients with IBD. The gut microbiota is clearly manipulated by dietary components such as n-3 polyunsaturated fatty acids (n-3 PUFA) and coniugated linoleic acid (CLA) which favorably reduce endotoxin load via shifts in the composition and metabolic activity of the microbial community. In particular, the beneficial effect of n-3 PUFAs and fermentable fiber, during the remission/quiescent phase of both CD and UC is highlighted. In fact, PUFAs are associated with a less grade of inflammation since they are metabolized to 3-series prostaglandins and thromboxanes and 5-series leukotrienes and, in addition, exert antiinflammatory effects when compared with their n-6 PUFA counterparts. In similar action to dietary n-3 PUFA, coniugated linoleic acid (CLA) have been reported to ameliorate intestinal inflammation in animal models of IBD. Currently is still unclear the role of the fibers in helping the remission of the disease. Data about the consumption of fiber are controversial. On one hand, dietary fibers can act as effective prebiotics by altering the intestinal microbial composition and promoting the growth of beneficial bacterial communities within the large intestine. On the other hand, fibers can promote diarrhea, pain and gas aggravating the clinical state. We suggest that the consumption of fermentable fibers may have a good impact on patients' health.

Key words: inflammatory bowel disease, IBD, nutrition, short chain fatty acids, microbiome, dysbiosis.

Riassunto. Le Malattie infiammatorie croniche intestinali (IBD) rappresentano delle patologie infiammatorie croniche a carattere ricorrente. I principali tipi di IBD sono il Morbo di Crohn e la Rettocolite Ulcerosa. In condizioni fisiologiche nell'intestino la microflora endogena, gli antigeni patogeni e la risposta infiammatoria di base sono mutualmente bilanciati. Un vasto numero e tipologia di fattori ambientali sono implicate

a vario titolo nella insorgenza delle IBD; tra questi ricordiamo il fumo di sigaretta, i fattori dietetici, lo stress psicologico, l'uso di farmaci antinfiammatori non steroidei, i contraccettivi, l'appendicetmia, l'allattamento al seno e le infezioni. Il support nutrizionale, unitamente alla terapia, ha un ruolo cruciale nel management delle IBD. Il microbiota intestinale è strettamente regolato da componenti introdotti con la dieta come gli acidi grassi polinsaturi, l'acido linoleico, che favoriscono la riduzione delle endotossine e regolano la attività metabolica della comunità microbica intestinale. Nello specifico, gli acidi grassi polinsaturi e le fibre fermentabili hanno un ruolo peculiare durante le fasi di remissione/quiescenza di malattia. Gli acidi grassi polinsaturi sono associati ad un basso grado di infiammazione mucosale. Queste caratteristiche sono state ampiamente evidenziate negli animali di laboratorio in cui è stata indotta la IBD. Quindi, una dieta ricca di acidi grassi polinsaturi ha evidenziato un miglioramento del quadro infiammatorio intestinale. Ad oggi, non conosciamo bene i specifici meccanismi biomolecolari antinfiammatori che le fibre esplicano sulla mucosa intestinale e che inducono la fase di remissione. Le fibre introdotte con la dieta esplicano una fattiva azione pre-biotica che promuove la crescita di una corretta flora microbica. In conclusion, fibre hanno una azione antinfiammatoria nei pazienti affetti da IBD con un miglioramento della storia clinica di malattia.

Parole chiave: malattie infiammatorie croniche intestinali, IBD, nutrizione, acidi grassi a catena corta, microbiota, disbiosi.

Introduction

IBD is an acronym that indicate a set of chronic recurrent disorders characterised by an excessive and prolonged intestinal inflammation. This group of diseases has been classified considering: location, severity and extent of the bowel involvement. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD shows a transmural granulomatous inflammation that can involve any segment of the intestine affecting all layers of the intestinal wall while UC is limited to the mucosa and superficial submucosa of the colon (1).

It is well established that a microflora imbalance is present in both leading to a modification of intercellular tight junctions responsible of mucosal permeability. As a consequence various antigens can penetrate within the intercellular space causing the activation of MALT and tissue damage.

In physiological conditions the gut is costantly exposed to various antigens, commensal microflora and pathogens and the inflammatory response is finely balanced (2). Anyhow in some individuals with genetic susceptibility an anomalous inflammatory response can arise due to the deregulation of the negative feedback mechanisms implicated in its self-regulation.

Recent data demonstrate that some single nucleotide polymorphisms can be associated with IBD. These mutations alter the expression of genes implicated in bacterial recognition, immune response and mucosal transport or polarity. It has been recognized that affected patients are more sensitive to bacterial invasion as they had lower levels of defensin gene expression in Paneth cells.

Generally, the aberrant inflammatory state causes an extensive tissue injury followed by edema, decreased mucous production, crypt cell hyperplasia, erosions and ulcerations. The function of the epithelial barrier appears impaired and the transmission of extracellular signals to the membrane is compromised.

Several studies suggest that nutrition may play an important role in the pathogenesis of the disease and may also modulate the intestinal inflammatory response showing a therapeutic effect (3).

This review is devoted to underlying the role of the diet and its potential benefits on the health of patients affected of moderate and mild forms of IBD.

Aetiologic and pathogenetic mechanisms of IBD

There is no single, established cause for these pathologies. The most widely accepted working hypothesis is that IBD represents a dysregulated immune response to common intraluminal antigens. It has been established a crucial pathophysiologic role for enteric bacteria. The onset of inflammation can be associated with a dysbalanced bacterial flora, with a pre-dominance of certain harmful species or bacterial metabolic products and an insufficient concentration of protective commensal species (4).

The etiopathogenesis of inflammatory bowel diseases (IBDs) is multifactorial and therefore cannot be explained only in terms of genetic susceptibility (5).

A vast number of environmental risk factors may influence the development of IBD, including smoking, dietary factors, psychological stress, use of non-steroidal anti-inflammatory drugs and oral contraceptives, appendectomy, breastfeeding, as well as infections .

We focus on diet as it can influence the species composition of the intestinal microbiota (6, 7).

Pre-illness diet could be a significant risk factor for the pathogenesis of IBD.

Recent analysis underline associations between IBD development and consumption of fiber, fruits or vegetables. Some authors demonstrated that the risk of CD is inversely associated with the intake of fruits and vegetables in a pediatric cohort and in a larger prospective adult study (8). Moreover, it seems that the higher intake of animal protein is also probably linked to the increased risk of CD. Western diet, characterized by high amount of sucrose, refined carbohydrate and omega-6 fatty acids and poor intake of fruits and vegetables, is therefore considered a trigger for this type of disorders. Recent evidences highlight also that foods are contaminated by natural contaminants such as dust and additives which may be antigenic (9, 10). Correlations studies from the Japanese area demonstrate an increasing incidence of CD within the population due to the progressive changes in diet habits associated with a massive amount of animal fat especially v-6 polyunsaturated fatty acids (PUFAs) (11, 12).

Nutrition therapeutic approaches: dietary interventions

Undernutrition has been often reported in patients with inflammatory bowel disease (IBD), particularly in patients with active Crohn's disease. The mechanisms standing behind malnutrition include reduced oral intake, increased energy requirements due to systemic inflammation, poor digestion, malabsorption due to chronic inflammation, and (mainly in CD patients) previous surgical resection or bypass of the bowel and protein-dispersion (13).

Factors that contribute to decreased food intake, in particular, include loss of appetite, hunger and depressed mood (14).

It is important to distinguish the difference between nutrition, requirements likely to prevent or delay development or early progression of the disease from secondary effects associated with late stage complications of IBD, especially malnutrition (15).

In quiescent IBD energy and substrate metabolism is normal or shows the typical changes of a shortage of energy intake with a decrease in carbohydrate and an increase in fat oxidation. During the active phase patients develop a mixed picture of an inflammatory reaction and malnutrition with slight increases in energy expenditure and a relative increase in fat oxidation and decrease in carbohydrate oxidation. These changes are, however, quickly reversible when patients are given nutritional support (16).

Nutritional support is adequate as disease modifying therapy for growth failure in children or adolescents with active small bowel disease (grade A). It may be used in preference to steroids, immunomodulators, or surgery for any patient with active disease (grade B), or for those unresponsive to mesalazine or in whom corticosteroids are contraindicated (grade C).

It can be considered as adjunctive therapy for any malnourished patients (grade C), or for those who have difficulty maintaining normal nutritional status (grade C).

Nutritional support is also appropriate for those with intestinal partial obstruction awaiting surgery (grade C), or severely symptomatic perianal disease (grade C), or those with postoperative complications. Enteral nutrition is preferred when the patient's condition permits (grade C).

Serum vitamin B12 is best measured annually in patients with ileal CD (grade C) (17)

Malabsorption rather than dietary insufficiency is the likely main underlying mechanism leading to fat-soluble vitamin deficiencies which, in turn, can be associated with metabolic bone disorder (13).

A wide array of vitamin and mineral deficiencies occurs in inflammatory bowel disease, with varying degrees of clinical significance (18).

The most striking feature is the identification of a low serum folate level and, to a lesser extent, a low serum vitamin B12 level.

Other nutritional deficiencies that can be found are iron, zinc and selenium.

Zinc, in particular, is crucial in patients with Crohn's disease presenting persistent fistulas because it play an essential role in wound healing. Moreover, it may be protective against free radical-mediated cellular damage since it is a co-factor for superoxide dismutase.

Nutrition has an important role in the management of patients with IBD. It is able to correct macro and micronutrient deficiencies in malnourished individuals, reverse the physiopathological consequences of such deficiencies, exerte an anti-inflammatory therapeutic effect. The possibility of using a nutritional approach as primary treatment of IBD allow the abolition of the use of corticosteroids and other immunomodulating drugs, none of which are free from systemic haematologic, metabolic and/or nutritional side effects (19-25).

It is thought that dietary products may modulate intestinal inflammation through: direct antigenic effect, alteration of gene expression, regulation of inflammatory mediators (e.g. eicosanoids), changes in the composition of the enteric flora and effects on gut permeability.

For example, the gut microbiota may be manipulated by dietary components such as n-3 PUFA and coniugated linoleic acid (CLA) to favorably influence inflammatory disease risk by reducing endotoxin load via shifts in the composition and metabolic activity of the microbial community (8).

It seems that PUFA may ameliorate disease severity by activating one or several PPAR isoforms in the gut. An evident accelerated regeneration of intestinal epithelia is observed when this receptor is activated.

Different studies have shown that when consumed in sufficient quantities dietary fish oil results in decreased leukocyte chemotaxis, decreased production of reactive oxygen species and proinflammatory cytokines, and decreased adhesion molecule expression (26).

Several randomized, placebo-controlled, double-blind studies analyze the role of fish oil in inflammatory bowel disease. These trials indicate that fish oil is linked to a better clinical score, improved gut mucosal histology, improved sigmoidoscopic score, lower rate of relapse and decreased use of corticosteroids (27).

In recent years, special attention has been paid to fat and the lipid components of the diet as triggers of IBD. The discussion is focused mainly on the importance of essential fatty acids, in particular the relation between the fatty acids omega 3 and omega 6, where omega 6 activates inflammation while omega 3 restrain the inflammation, has been resumed (28).

This balance is better maintained if the consumption of grain and oils saturated by omega 6 acids is reduced and that of fat fish, nuts, seeds and vegetables is increased (29).

It is advisable that patients follow an healthy and varied diet.

Recently it has been established that Mediterannean diet, characterized by high levels of vegetables, fruits, olive oil, fish, grains, and nuts (30), was inversely associated with CD in both genders. Encouraging uptake of a Mediterannean diet may be desirable in protecting against IBD and other forms of chronic disease (8).

During acute phase of IBD prescribing a low-residue diet, poor in insoluble fiber, may be recommended particularly in individuals with stricturing CD or severe UC attacks.

The beneficial effect of n-3 polyunsaturated fatty acids (PUFAs) and fermentable fiber, during the remission/quiescent phase of both CD and UC was highlighted. PUFAs are associated with a less grade of inflammation since they are metabolized to 3-series prostaglandins and thromboxanes and 5-series leukotrienes and, in addition, exert antiinflammatory effects when compared with their n-6 PUFA counterparts (31).

Fermentable fiber generates much less residue than insoluble fiber, and it is fermented by colonic microflora, generating short chain fatty acids (SCFA), mainly butyrate, than can be of benefit in IBD. In

fact, there are in vitro-evidences suggesting that butyrate is able to down-regulate the production of pro-inflammatory cytokines, to promote the restoration of intracellular Reactive Oxygen Specie (ROS) balance, and the activation of NF-kB. Moreover, according to several in vivo-studies, rectal administration of butyrate or mixtures of SCFA were reported to decrease inflammation in patients with active UC. In similar action to dietary SCFA, coniugated linoleic acid have been reported to ameliorate intestinal inflammation in animal models of IBD. In contrast to corticosteroids, CLA suppresses gut inflammatory responses while enhancing antigen specific responsiveness of T cells against viral and bacterial pathogens. A significant study demonstrate that pig with colonic lesions treated with diets supplemented with soybean oil, conjugated linoleic acid, fish oil or CLA and fish oil exhibit a beneficial effect of CLA in both disease severity and kinetics of appearance of clinical signs, whereas n-3 PUFA failed to protect from the disorder but favored remission (32).

Available data about nutritional interventions do not always match due to the incomplete knowledge of pathogenic mechanisms underlying IBD development. Further studies are therefore needed to improve nutritional therapeutic approach.

Current evidences suggest that the use of prebiotics can be positive in the treatment of IBD.

Prebiotics are non-digestible food ingredients that stimulate the growth and/or activity of bacteria in the digestive system confering benefits upon host wellbeing and health . Nowadays, only two dietary oligosaccharides meet the criteria for prebiotic classification: inulin and oligofructose, which are natural food ingredients or dietary fibers present in certain plants as storage carbohydrates. Many other food components have been shown to have prebiotic activity even though they do not fulfill the required criteria: (a) resistance to gastric acidity, hydrolysis by mammalian enzymes and absorption in the upper part of the gastrointestinal tract; (b) fermentation by beneficial bacteria in the intestine; and (c) selective stimulation of growth and/or activity of colonic microflora toward a healthier composition (33).

Prebiotics and fiber carbohydrates are involved in different protective mechanisms such as increasing amount of short chain fatty acids (SCFAs), changes in the intestinal microbiota, improvement of the intestinal barrier and regulation of the mucosal and systemic immune response. Dietary prebiotics can be applied to the prevention of human enteric inflammatory disorders while maintaining optimal levels of immune surveillance. Recent studies showed how prebiotics increased the number of beneficial bacteria such as lactobacilli and bifidobacteria, while decreasing the disease-causing bacteria in both animal models and human clinical studies (42, 44). Moreover, prebiotics can also provide resistance to colonization by pathogenic bacteria by inhibiting the adherence of pathogens to the gut epithelium (34).

The oral intake of probiotics and synbiotics is important because they are able to prevent an injury of the mucosa associated with the consumption of dairy products and species of grain containing gluten. Probiotics yoghurt, bread enriched with fibre and B-vitamins and breakfast cereals are good nutritional products with anti-inflammatory effects (28, 35-37).

Maintenance of remission: dietary modification

Prevention of relapse either of the disease or of a malnourished state is an important area of nutritional research. There is a lack of a safe, long-lasting modality for relapse prevention. Exclusion diets are of use particularly for maintenance of remission. Despite early ideas about the involvement of sugars in the etiology of CD, the omission of sugar has not been found to be of benefit. Omega oil has shown promising results, particularly in reducing inflammation in UC, and to a lesser degree, in CD (38, 42).

"Elimination" involves remission induced by elemental feeds, followed by careful and slow 'reintroduction' of single food types to enable identification of those that precipitate symptoms. An alternative is the low-fibre, fat-limited exclusion (LOFFLEX) reintroduction diet, which involves a faster reintroduction phase of varied food types, instead of single food types, after EN-induced remission.

A food reintroduction diet can be used to identify any foods that may induce symptoms or cause problems. Examples of food reintroduction diets in-

clude general elimination diets, and the LOFFLEX diet (LOw Fibre, Fat Limited, Exclusion diet) which excludes foods high in fat and fibre, before slowly reintroducing them. Initially a diet of bland foods is prescribed to the patient and subsequently foods are introduced in large quantities so that if there is a reaction it becomes obvious (13).

Another alternative is known as the "FODMAP" diet. FODMAP is an abbreviation for a group of molecules found in food called fermentable carbohydrates. The initials stand for 'Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols'. These molecules are not opportunely digested, so they pass into the colon acting as a food source for bacteria. The bacteria digest the FODMAPs and in doing so can cause symptoms such as bloating and wind (39).

Cutting out food containing FODMAPs is thought to alleviate these symptoms. Examples of FODMAP-containing foods include fructose (apples, pears, corn syrup), lactose (dairy products, soft cheeses), fructans and galactans (wheat, cabbage, broccoli, watermelon) and polyols (apples, apricots, cauliflower, sorbitol).

Now is still unclear whether dietary exclusion–reintroduction diets or FODMAP diets maintain remission through persistence of mucosal healing or are of predominant symptomatic benefit by alleviating 'functional' symptoms. Probably FODMAP diets reduce the osmotic load and bacterial fermentation associated with the food delivered (40, 41), rather than having a primary anti-inflammatory effect.

Conclusions

Crohn's disease (CD) and ulcerative colitis (UC) show the presence of a condition of persistent phlogosis of the intestinal mucosa. These diseases have common pathogenetic and epidemiological characteristics but, at the same time, have some specific aspects suggesting that they must be considered different clinical entities. These disorders occur with latency periods alternated with periods of exacerbation.

The high consumption of refined carbohydrates, mainly sugar, in patients who experienced IBD may be one risk factor. This association would explain the high incidence in industrialized countries.

It has been hypothesized that the increasing incidence of IBD is linked to social and economic development and alteration of lifestyle on the Western model (dietary changes, smoking, use of oral contraceptives and stress).

A diet characterized by high amounts of sucrose, refined carbohydrates, fatty acids omega-6 (known as potential phlogogenic-oil sunflower seeds, soy, corn, nuts, and some margarines), few fruits and vegetables, compared to those who had greater consumption of fruits, vegetables and complex carbohydrates seems to be related to the development of these disorders . It was also suggested that the "urban diet" containing contaminants in food, such as dust, inorganic microparticles, additives, heavy metals which, combined with some components in the intestinal lumen favors the formation of particles capable of damaging the intestinal mucosa and to pass into the systemic circulation.

The food, acting as luminal antigen, has been considered one of the causal factors in the immunopathogenesis of the disease but it is unclear whether the antibodies against the food is the primary cause of the disease or whether they do not develop secondarily to the state of intestinal inflammation. Malnutrition is often present in these patients and numerous interventions are often used.

Attention to nutrition-related issues must be considered central to the management of patients with inflammatory bowel disease. The use of nutrition as primary treatment in inflammatory bowel disease can have great importance, both in the onset of the disease and in the duration of periods of remission.

Proper nutrition helps the body and to better tolerate the therapies that are made by reducing the side effects and giving the opportunity to the patient to remain in good health.

Currently is still unclear the role of the fiber in helping the remission of the disease. Data about the consumption of fibre are controversial. On one hand, dietary fibers can act as effective prebiotics by altering the intestinal microbial composition and promoting the growth of beneficial bacterial communities within the large intestine.

Some authors reported a positive effect associated with the production by colonic microflora of short

chain fatty acids (SCFA), able to down-regulate the production of pro-inflammatory cytokines, to promote the restoration of intracellular Reactive Oxygen Specie (ROS) balance, and the activation of NF-kB.

On the other hand, fibers can promote diarrhea, pain and gas aggravating the clinical state. We suggest that the consumption of fermentable fibers may have a good impact on patients' health.

The identification of certain SNPs associated with the disease allow us to detect if an individual is a carrier of markers of disease susceptibility. The knowledge of the presence of a specific genotype may suggest what types of food are linked with a well-being state. Further studies are therefore needed to improve nutritional therapeutic approach.

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