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Nutritional Therapy for Inflammatory Bowel Disease

Rok Orel, Evgen Benedik, Janez Eržen,
Anija Orel and Darja Urlep

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Abstract

The components of a diet influence intestinal microbiota, epithelial barrier function, immune system, and many other factors that play important role in both development and treatment of inflammation in gastrointestinal tract. We briefly review potential role of specific dietary compounds as a risk or protective factor, but we predominantly concentrate on nutritional status and nutritional intervention in patients with inflammatory bowel disease. Besides exclusive enteral nutrition as a potential first-line treatment in active Crohn's disease, other nutritional therapeutic modalities such as partial enteral nutrition, parenteral nutrition, diets based on carbohydrate modifications, anti-inflammatory diet, and the use of specific dietary compounds with anti-inflammatory properties, known as pharmaconutrition, are presented.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, nutrition, nutritional therapy

1. Introduction

The exact etiology and pathophysiologic mechanisms of inflammatory bowel diseases (IBD) are not completely explained, but the complex interplay among genetic background, environmental factors, intestinal microbiota, and immune system seems to be implemented. The incidence and prevalence of both types of IBD, Crohn's disease (CD) and ulcerative colitis (UC), has dramatically increased in western countries and in developed Asian countries in the last 50 years [1]. In addition, several epidemiologic studies revealed that the incidence of IBD in descendants of immigrants from the parts of the world with low incidence to the countries with high incidence resembles the one of the native population and not of the country of their origin [2, 3]; these points to the crucial role of environmental factors/changes in IBD

epidemics. The potential influences of specific factors such as changes in hygiene/sanitation, decreased exposure to infectious agents, smoking, water and air pollution, psychological stress, and an increased use of certain drugs have all been proposed and are reviewed elsewhere [4, 5]. An increasing body of evidence is linking IBD with diet.

Dietary constituents and their proportions can affect human physiology directly. However, intestinal microbiota, recently recognized as an essential component of metabolism, immune and neuroendocrine regulation, is also importantly influenced by diet. For example, intestinal microbiota of African children, whose diet is based on fiber-rich, plant-derived diet, was found to be vastly different to microbiota of their European peers, who consume diet rich in sugar, dairy, fat, and protein [6]. Animal studies revealed that change from low-fat, high-fiber diet to “Western style” diet rich in fat and sugar resulted in substantial shift in microbiota within a single day [7]. Changes in composition and function of intestinal microbiota because of specific dietary patterns may lead to a state not favorable for host organism, defined as dysbiosis. Numerous studies have shown that gut microbiota of IBD patients substantially differs from the one of healthy individuals and that these changes may play a crucial role in the development and activity of the disease [8]. Enteric microbiota plays an essential role in metabolizing nutrients, especially those not completely digestible by human digestive enzymes, such as fiber, resulting in production of diversity of biologically active components, such as short chain fatty acids (SCFAs) and intestinal gases. A study from Japan showed that people living in rural areas consuming traditional Japanese food have more abundant Bifidobacteria, which are recognized as an important producer of SCFAs, than urban population eating western-type diet [9]. Western-type diets, rich in saturated fat and protein and poor in plant fiber, result in depletion of Firmicutes, which are involved in metabolism of plant polysaccharides, and decrease in SCFA production [10]. On the other hand, this kind of diet promotes growth of proteolytic bacteria, such as *Bilophila wadsworthia* and other bile tolerant microbes, which use proteins and bile acids as a source of organic sulfur and produce hydrogen sulfide (H₂S). H₂S can be genotoxic, modulate expression in cell cycle progression, trigger inflammatory response, and impair DNA repair [8].

Direct effects of relative abundancy/deficiency of specific nutrients and changes in composition and functioning of intestinal microbiota can lead to impairment of intestinal barrier function, including decreased resistance to invasion of pathobionts, dysfunction of innate, and adaptive immune system that finally results in chronic inflammation and tissue damage characteristic for IBD.

In this chapter, we try to review current knowledge about the effects of specific food components on IBD concentrating on clinical evidence about efficacy of different dietary interventions in IBD patients.

2. Role of specific food constituents

Most of our knowledge about the influence of specific food ingredients on intestinal function, development of inflammation, and IBD in particular originates either from animal model experiments or from epidemiological studies.

2.1. Fats

There is a growing evidence that some types of fat act pro-inflammatory, while the others protect against development of intestinal inflammation. Several big epidemiologic studies, such as European Investigation into Cancer and Nutrition Study (EPIC) and the Nurses' Health Study have pointed to an increased risk of IBD among people who consume greater amounts of meat and fats, particularly polyunsaturated fatty acids and omega-6 fatty acids [11–13]. The EPIC study revealed an association between greater consumption of an omega-6 polyunsaturated fatty acid (PUFA), linoleic acid, present in high concentrations in red meat, cooking oils, and margarine and higher incidence of UC. In contrast, people who consumed higher levels of omega-3 PUFA docosahexaenoic acid (DHA) were less likely to develop UC [11–13]. Similarly, consumption of large quantities of nuts and fish, which are rich in omega-3 PUFA such as DHA, eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA), was shown to lower the risk for CD [14]. Omega-3 fatty acids were shown to have an anti-inflammatory, antithrombotic, antiarrhythmic, and hypolipemic effect [15]. There was also a significantly reduced risk for CD when ratio of long-chain omega-3/arachidonic acid was high in the consumed food [14].

In conclusion, it seems that diet rich in animal fats and particularly omega-6 PUFA promotes dysbiosis and intestinal inflammation that may lead to development of IBD in genetically susceptible hosts. On the other hand, omega-3 PUFA seems to play a protective role and may even promote anti-inflammatory mechanisms.

2.2. Proteins

As already mentioned, several epidemiologic studies revealed an association between consumption of large quantities of meat and increased risk for IBD [11–13]. It is not clear whether this association was only due to increased intake of fats or also of proteins, as the results of the studies regarding the role of proteins in IBD were conflicting [13]. In one study, high intake of proteins found in meat but not in dairy products was found to be positively associated with IBD [16].

Among the specific proteins and peptides, the effects of gluten-derived proteins were particularly attentive. In animal model, gluten-fortified experimental diet induced chronic ileitis [17]. They found reduced occludin expression levels, and these findings suggest a negative role of gluten on intestinal barrier integrity. Experiments on intestinal epithelial cell lines showed that gliadin induces an increase in intestinal permeability due to zonulin release by binding to the chemokine receptor CXCR3 [18]. Zonulin is the physiologic modulator of tight junctions that regulate intestinal permeability through the epithelial paracellular pathway. Its upregulation in genetically susceptible individuals may lead to different immune-mediated diseases [19]. It was observed that intestinal permeability increased after gliadin exposure not only in patients with celiac disease or nonceliac gluten sensitivity but, although to a lesser extent, also in healthy subjects [20].

2.3. Carbohydrates

Many epidemiological studies pointed out that excessive consumption of simple carbohydrates, refined sugars, sweet carbonized drinks, or even artificial sweeteners might represent

a risk factor for the development of IBD; however, as many others failed to prove this association [21]. Individual studies even showed that low complex carbohydrates and low refined sugar intake significantly improved laboratory inflammatory markers and fecal calprotectin in patients with IBD [22].

On the other hand, consumption of vegetables and fruits rich in both soluble and insoluble fiber has been shown to be negatively associated with IBD [14, 23, 24]. Animal studies confirmed that plant polysaccharides and poorly digestible fibrous plant components have reduced features of experimental colitis [25]. Fermentable fiber is fermented by saccharolytic gut microbiota, resulting in increased production of SCFAs. SCFAs, especially butyrate, are utilized not only as fuel sources for colonocyte that results in enhancement of the intestinal barrier, but also possess anti-inflammatory effect, mainly through inhibition of the production and release of inflammatory mediators [26, 27]. In addition, some vegetables like broccoli and cabbage are thought to activate the aryl hydrocarbon receptor (AhR), which is highly expressed by intestinal intraepithelial lymphocytes and is involved in immune regulation and defense against attacks of luminal microorganisms [28]. Overall, refined and processed carbohydrates and intake of sweetened beverages are thought to be risk factors for developing IBD, while complex carbohydrates like vegetables, fruit, and fiber showed to be protective.

2.4. Food additives

It has been hypothesized that emulsifiers, detergent-like molecules that are a ubiquitous component of processed foods, can disrupt intestinal mucus layer, increase intestinal permeability, and enable bacterial translocation across epithelia [29]. In mice, relatively low concentrations of two commonly used emulsifiers, carboxymethylcellulose and polysorbate-80, induced low-grade inflammation in wild-type hosts and promoted robust colitis in mice predisposed to IBD [30].

Maltodextrin, a polysaccharide derived from starch hydrolysis, was found to promote adherent-invasive *E. coli* (AIEC) biofilms and increase adhesion of AIEC strains to intestinal epithelial cells and macrophages [31]. Strains of AIEC have been isolated from the ileum and the colon of CD patients [32, 33].

Therefore, consumption of maltodextrin and emulsifiers may possibly support growth of intestinal pathobionts, such as AIEC and their translocation across epithelial barrier, where they could survive in macrophages and lead to chronic inflammation.

3. Nutritional status of IBD patients

According to available data, malnutrition affects 65–75% of patients with CD and 18–62% of patients with UC [34, 35]. In pediatric IBD patients, malnutrition frequently results not only in weight loss but also in growth retardation [36, 37].

Main reason for malnutrition in IBD patients is insufficient food intake due to the loss of appetite and avoidance of certain foods presumably worsening the symptoms, resulting in prolonged restrictive diets [38, 39]. Intestinal inflammation and inflammatory cytokines

released from immune cells can damage epithelial integrity and impair absorption of nutrients. In addition, bacterial overgrowth and increased intestinal mobility may contribute to malabsorption [40, 41]. Fat and fat-soluble vitamin absorption may be especially impaired in CD patients when terminal ileum is seriously affected due to the biliary salt malabsorption [42]. Some of the medications used for IBD treatment, such as glucocorticoids, sulfasalazine, and immune system suppressants, could have a negative impact on micronutrient absorption and utilization [34, 42]. It should be noted that IBD patients with active inflammation have increased metabolic rate, which leads to increased energy expenditure [36, 37, 43].

An important aspect of malnutrition in IBD patients is alteration of body composition. Fat mass (FM) consists of adipose tissues (both visceral and subcutaneous) while fat-free mass (FFM) consists of water, proteins, minerals, and other components [35]. Clinical studies revealed an important reduction of both FM and FFM in active phase of IBD. However, it was also reported that FM was frequently recovered during remission phase, while FFM remained depleted [35].

Malnutrition, immobility, low protein synthesis, and increased proteolysis due to inflammation are the main mechanisms leading to sarcopenia, a progressive and generalized loss of skeletal muscle mass and strength with risk of poor quality of life and physical disability [44]. Sarcopenia has various negative health consequences such as pathological fractures due to bone demineralization, cardiovascular disease, and higher probability of hospitalization [44].

Several studies reported that despite aforementioned causes leading to malnutrition in IBD, one-third of the patients are obese, the proportion is similar in CD and UC patients [45, 46]. Obese IBD patients do not have worst long-term clinical outcome than normal weight patients [47]. However, simultaneous presence of sarcopenia and obesity, so-called sarcopenic obesity, is related to a fast functional decline of patient's status, with a high risk of morbidity, disability, and mortality [44].

Micronutrient and vitamin deficiencies are common in IBD patients. Preventions of those deficiencies are mandatory for avoidance of possible clinical complications. The most common micronutrient deficiencies described in IBD patients are known for iron, calcium, selenium, zinc, magnesium, and vitamins, in particular B12, folic acid, A, D, and K [34, 42].

One of the important features of IBD is anemia. Its prevalence in pediatric patients is up to 70% and in adult patients up to 50% [48]. The most frequent cause of anemia in IBD patients is iron deficiency (prevalence estimated in 36–90% of CD and UC patients), following vitamin B12 (prevalence estimated in 22% of CD and 3% of UC patients) [34, 49], and folic acid (vitamin B9) deficiencies (prevalence estimated in 29% of CD and 9% of UC patients) [50]. These deficiencies are the consequence of bleeding from mucosal lesions, inadequate dietary intake, impaired absorption and utilization, surgery (ileal resection greater than 60 cm will develop B12 deficiency), systemic inflammation, and medications [37, 50, 51].

Calcium and Vitamin D deficiency are often in IBD patients, especially in those with duodenal and jejunal disease, when their absorption is disturbed [34, 42]. Their prevalence is 70% in CD and 40% in UC patients. Besides its influence on bone metabolism, vitamin D have important role in preserving mucosal integrity and mucosal healing capacity. In case of its deficiency, the

risk for mucosal damage and for IBD is higher [34, 42]. It was shown that high levels of active vitamin D not only reduce the risk of developing CD, but also the risk of developing UC [52, 53].

Vitamin A deficiency in IBD patients is high up to 90%. Vitamin A deficiency results in impaired wound healing, night blindness, and xerophthalmia [34, 42].

Vitamin K deficiency in IBD patients is also reported, but the prevalence is unknown. Most important source of vitamin K is intestinal production by gut microbiota. Dysbiosis, use of antibiotics, and malabsorption may contribute to this deficiency [34, 42].

Inadequate dietary intake and chronic loss because of diarrhea are the main reasons for selenium, zinc, and magnesium deficiencies in IBD patients for which the exact prevalence is not known. Symptoms associated with deficiencies include bone health impairment, cartilage degeneration, fatigue, and poor wound healing [34, 42].

4. Nutritional intervention

EEN has been evaluated in a number of clinical studies including randomized controlled trials (RCTs) that compared EEN to CS in adult and pediatric populations of patients with active CD. To date, eight meta-analyses have been published on the efficacy of EEN versus CS. Among these meta-analyses, three of them were performed exclusively on the pediatric population while others included adult patients as well. While meta-analyses of adult studies have suggested better efficacy of CS, pediatric studies have shown that EEN is at least as effective as CS in inducing remission and is superior to CS in improving nutritional status and growth recovery without adverse side effects [54].

The main goals of nutritional intervention in IBD patients are treatment and prevention of malnutrition, treatment of active inflammation and maintaining remission in Crohn's disease, and symptomatic treatment in specific situations [55].

Regular evaluation of nutritional status, early detection of specific deficits and specific risk factors are crucial for adequate nutritional treatment. Anthropometric measurements and basic laboratory tests, such as hemoglobin concentration and markers of inflammation, should be checked regularly at every visit, while the frequency of albumin, ferritin, vitamin, and trace element concentration checkout depends on the activity of the disease, but should be done at least once a year when the disease is quiescent [55]. Periodical evaluation of detailed body composition and bone mineral density is recommended. Bioimpedance (BIA) and dual-energy X-ray absorptiometry (DEXA) are considered as the gold standard for measuring body composition [56]. A dietary history and, sometimes, prospective dietary record are necessary to get a good estimate of food intake. We should be aware that many patients develop special dietary habits due to their belief that consumption of specific foods (e.g., dairy, meat, fruit, and vegetables) results in symptoms or even worsen the disease course, which may additionally contribute to the development of nutritional deficiencies [57].

With the exception of the ECCO/ESPGHAN recommendations to use exclusive enteral nutrition as a first-line therapeutic approach in children with active CD [58], the strict guidelines for nutritional

intervention in IBD does not exist. However, many different dietary approaches have been developed and studied, with intention to alleviate patients' symptoms or even treat the disease.

4.1. Exclusive and partial enteral nutrition

Exclusive enteral nutrition (EEN) means that 100% of a person's nutritional requirements is provided by a liquid nutritional formula either orally or via a feeding tube. Numerous studies have shown that the treatment of active CD with exclusive enteral nutrition (EEN), especially in children, is as effective as corticosteroids in inducing remission. EEN, used as monotherapy, can induce remission in up to 80% of patients with active CD [59, 60]. It is well established that treatment with EEN is capable of achieving mucosal healing. On the contrary, corticosteroids have poor ability to induce mucosal healing [61]. In comparison to therapy with drugs, EEN has no adverse effects and, even more importantly, improves growth, and reverses malnutrition [58]. Therefore, according to the ECCO/ESPGHAN guidelines for treatment of pediatric CD patients, EEN is recommended as a first-line treatment in children and adolescents with active CD [58]. Meta-analysis of the results of the studies using ENN for the therapy of active CD in adult CD patients indicated that it was less effective than steroids in inducing remission; however, this conclusion was based on intention-to-treat analysis [62]. However, when only the results of the patients who completed the course of EEN were analyzed, the remission rates were comparable to those achieved by steroids [63].

EEN is usually provided for 6–8 week, and then a normal diet is gradually reintroduced. Enteral formulas are differentiated by the structure of their protein content. Elemental diets contain no intact protein, but only amino acids. Semielemental diets are based on peptides of varying lengths. Polymeric formulas contain whole proteins and are therefore more palatable in comparison with elemental diets [64]. Protocols of EEN may be different regarding the composition of the enteral formula and route of administration. Elemental diets often require a feeding tube to administer due to their poor palatability. In addition, polymeric formulas are reported to cost less. Various studies and a large meta-analysis later demonstrated that polymeric formulas were as effective as elemental formulas [65].

Although EEN has been shown to be efficacious, its mechanism of action remains unknown. Possible mechanisms include a change in gut microbiota, bowel rest, dietary antigen elimination, improvement in the nutritional status, and potential anti-inflammatory properties of specific ingredients of enteral formulas. Currently, the modification of gut microbiota seems to be the most probable proposed mechanism for ENN efficacy. The next very important mechanism may be associated with exclusion of potentially harmful food ingredients [60].

One of the proposed challenges influencing acceptance of EEN is the restriction of other oral food intake, which may seriously limit compliance with the EEN protocol [66]. Therefore, studies on partial enteral nutrition (PEN), which allows patients with active CD to consume a part of their daily caloric needs from a normal diet, have been conducted.

The results reported from the first study on the efficacy of PEN did not indicate that PEN providing 50% of caloric needs by formula was effective for induction of remission in pediatric CD [67]. However, the results of some recently published studies are more promising. Israeli

authors combined PEN with Crohn's Disease Exclusion Diet (CDED) [68]. CDED is a structured diet, which excludes animal fats, milk and dairy, gluten, and all processed and canned foods, which contain additives, especially emulsifiers and maltodextrin. The authors hypothesize that the major mechanism leading to response to EEN used in children with active CD is exclusion of specific dietary factors, which may have a negative impact on mucous layer, intestinal permeability, and colonization with adherent-invasive E coli (AIEC). The study protocol allowed patients to consume up to 50% daily calories from CDED. Response and remission were obtained in 78.7 and 70.2% patients, respectively. Different approaches using PEN was developed at the Children's Hospital of Philadelphia [69]. The patients receive 80–90% of their energy input from EN, but they were allowed to consume remaining calories from a normal diet. Retrospective analysis revealed remission rate of 65% and response rate of 87%, which is comparable with the remission rates from the studies using EEN. Further studies are needed to elucidate the efficacy of this treatment approach.

One of the problems of CD therapy with EEN is that disease relapses relatively frequently soon after stopping EN when the patients are not receiving maintenance therapy. Several studies using PEP as a maintenance therapy either alone or in combination with drugs were performed in both pediatric and adult patients with CD. The results of the majority of these studies, as well as their systematic reviews [70–72], showed that the relapse rate during observational period was significantly lower in patients using PEP compared with those consuming regular unrestricted diet and that efficacy of maintenance therapy with PEP might be comparable to standard therapy with drugs. In addition, nutritional status as well as linear growth of children with CD was found to be better in those using PEP during remission in comparison with patients on regular diet [73].

4.2. Total parenteral nutrition

In the 1980s, total parenteral nutrition (TPN) was used to treat patients with moderate to severe CD. The aim of TPN as primary therapy for IBD was to achieve bowel rest, to correct nutritional deficits, and to remove antigenic mucosal stimuli [74, 75]. In the 1990s, treatment with exclusive enteral nutrition (EEN) was shown to have similar or even better results in terms of remission rate in active CD disease. When TPN and ENN are compared, TPN is associated with higher costs and significant risk of serious adverse events including sepsis. Therefore, TPN should be restricted to patients who cannot be adequately fed by enteral route, mainly those with gut failure and short-bowel syndrome [76].

According to recent ESPEN guidelines on clinical nutrition in IBD, TPN is indicated only when EN has failed or it is impossible to be administered [77].

4.3. Diets based on carbohydrate modifications

Low-fiber or even so-called low-residue diets are frequently recommended during acute exacerbations of IBD [78]. While a low-fiber diet excludes only insoluble fiber, a low-residue diet requires exclusion of not only all vegetables, fruits, whole grains, legumes, but also dairy products and fibrous meat [79]. A basic idea behind these diets is that they reduce the volume and frequency of stools as well as the risk of intestinal obstruction. Although these diets are

usually prescribed for a short-term use, many patients continue with them for a long period of time. Objective studies failed to find any difference in severity of symptoms, number of complications, and needs for hospitalization or surgery between patients using such diets and those consuming unrestricted diet [80]. As already mentioned, indigestible carbohydrates, especially the fermentable ones may play an important protective role in IBD, as they represent the main substrate for production of SCFAs by intestinal bacteria. The only patients that may benefit from fiber restriction are those with strictures and obstructive symptoms.

Significant proportion of IBD patients also suffers from functional irritable bowel syndrome-like symptoms even in remission independently of actual level of the inflammation [81]. Low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet results in symptom relief in many of such patients [82]. However, low-FODMAP diet is very restrictive, so it should be carefully planned by professional dietetics to prevent development of specific nutritional deficiencies. In addition, the influence of low-FODMAP diet on the microbiome, metabolism, and inflammation in patients with IBD is still unclear.

On the other side, several studies using fiber-rich supplements such as wheat or oat bran [83, 84], psyllium [85, 86], and germinated barley foodstuff [87, 88] revealed their efficacy in symptomatic improvement and in decreasing disease activity indices either in CD or UC patients. Moreover, reduced concentrations of inflammatory cytokines, such as TNF- α , IL-6, and IL-8, pointed to the possible anti-inflammatory effect of dietary fiber, probably through their influence on microbiota and SCFA production [89].

Another diet, based mainly not only on restriction of specific carbohydrates but also on some other foods, called the specific carbohydrate diet (SCD) was developed in the 1920s [90]. Since then, this diet has been used in a variety of different conditions, including IBD, irritable bowel syndrome, celiac disease, and autism [91]. The SCD restricts all carbohydrates except monosaccharides: glucose, fructose, and galactose. This diet is based on a hypothesis that complex carbohydrates may induce intestinal dysbiosis resulting in the development of inflammation [92]. While fresh or cooked fruits, vegetables, and legumes are in general acceptable, all grains as well as potatoes should be omitted. In more restrictive versions of SCD, even milk and dairy products, refined sugar and artificial sweeteners, corn, and maple syrup are prohibited. In addition, all otherwise permitted food should not be processed (canned, smoked, etc.) and should not contain potentially harmful additives [91]. Several relatively small studies found out that SCD alone without taking medications may lead to clinical improvement, reflected by symptom disappearance and significant reduction of laboratory markers of inflammation, in some patient with active CD [91, 93]. However, recently published study using endoscopic evaluation before and after the treatment with SCD revealed that despite some clinical effect, complete mucosal healing was never achieved [94].

4.4. IBD-anti-inflammatory diet

Recently, an investigator group from USA developed the IBD-anti-inflammatory diet (IBD-AID) to be offered to IBD patients who are refractory to pharmacological therapy, or for whom the treatment is not as effective as desired [95]. The IBD-AID has five basic components. The first is the restriction of certain carbohydrates, including lactose, and

refined or processed complex carbohydrates. The second is the use of pre- and probiotics and foods rich in the components that help to restore the balance of the intestinal microbiota (e.g., soluble fiber, leeks, onions, and fermented foods). The third is distinctive use of saturated, trans-, mono-, and polyunsaturated fats. The fourth principle is to review the overall dietary pattern, detect missing nutrients, and identify specific food intolerances. The last component is a modification of food textures to improve absorption of nutrients and to minimize the adverse effect of intact fiber. In practice, the IBD-AID consists of lean meats, poultry, fish, omega-3 eggs, particular sources of carbohydrates, select fruits and vegetables, nuts, and legume flours, but restricts the consumption of wheat, rye, and barley products as well as milk and dairy products other than yogurt, kefir, and limited aged cheeses. A retrospective review of their case series including both patients with CD and UC revealed that approximately one-third of the patients chose not to attempt this diet, while the vast majority of those who followed the diet for 4 weeks or more reported symptom reduction and were able to discontinue at least one of their prior IBD medications [95]. However, randomized clinical trials are needed to properly elucidate the efficacy of this treatment regimen.

4.5. Pharmaconutrition

Several studies have shown that specific nutrients when supplemented in quantities exceeding their nutritional role may affect the immune system, metabolism, and gastrointestinal structure and function. Such examples are some amino acids like glutamine, arginine and tryptophan [96], omega-3 PUFA [97], vitamin D [98], and curcumin [99].

Glutamine and arginine are thought to be immunomodulatory and could be involved in mediating responses to metabolic stress. Studies on animal models revealed that they improved biochemical and clinical parameters of chemical-induced colitis [100]. Histamine, a biogenic amine derived from the amino acid histidine, reduced symptoms of experimental immune-mediated colitis [101]. Similarly, threonine reduced features of colitis and enhanced intestinal mucus production, which in turn leads to better barrier function [102, 103]. Tryptophan, another essential amino acid, also possesses strong anti-inflammatory effect both by direct action on intestinal and immune system cells and indirectly serves as a precursor for serotonin and melatonin [103]. A detailed review on the effects of specific amino acids on intestinal inflammation can be found elsewhere [96]. Although these amino acids may have some positive effect in IBD patients, their efficacy has not been adequately studied yet.

Omega-3 PUFA negatively affects intestinal inflammation through several mechanisms. [97]. They can act as a substrate for anti-inflammatory eicosanoid production, as well as a substrate for the synthesis of resolvins, maresins, and protectins, engaged in resolution of inflammatory process. On the other hand, they reduce production of pro-inflammatory cytokines such as TNF- α , decrease expression of adhesion molecules and possess antioxidative and chemoprotective properties. The results of clinical trials using omega-3 PUFA in patients with either CD or UC were inconsistent. Cochrane review, considering the use of omega-3 PUFA for maintenance treatment published in 2011, revealed a small but significant benefit in CD, but not in UC patients [104].

Besides its role in calcium metabolism and bone mineralization, vitamin D is regarded as an important anti-inflammatory agent. It regulates immune cells trafficking and differentiation, intestinal permeability, and antimicrobial peptide synthesis [98]. Several studies revealed an inverse association between serum concentration of 25-hydroxy-vitamin D and mucosal inflammation in IBD patients [105, 106]. Therefore, supplementation in IBD patients with low serum level of vitamin D seems mandatory. In a randomized controlled trial, a maintenance dose of 1200 IU/day, regardless of vitamin D status at entry, reduced a relapse rate in patients with CD [107].

Curcumin is the active compound found in turmeric. It possesses anti-inflammatory, anti-oxidant, anticancer, and neuroprotective properties [99]. Several studies and systematic reviews reveal that supplementation with curcumin when provided simultaneously with medications is both effective and a safe option for maintenance treatment of UC [108, 109].

5. Conclusion

Nutritional intervention is an important part of the treatment in IBD patients. Goals of nutritional intervention exceed provision of energy, macronutrients, and micronutrients to ensure adequate nutritional status of the patients. Recognition of the ability of specific food ingredients to interfere with the disease mechanisms has led to the development of several therapeutic approaches based on a diet modification. However, only the effectiveness of exclusive enteral nutrition in active CD has been proven enough to find place in different international therapeutic guidelines. As this kind of diet is difficult to keep for a prolonged period of time, other potential options such as partial enteral nutrition and restriction or even exclusion of potentially harmful foods with simultaneous increased intake of food ingredients that potentially interfere with different pathologic mechanisms seem extremely promising. However, we need to confirm the efficacy and safety of these novel dietary approaches more firmly before recommending their routine use in an everyday clinical practice.

Conflict of interest

Authors have no conflict of interest.

Author details

Rok Orel^{1*}, Evgen Benedik¹, Janez Eržen¹, Anija Orel² and Darja Urlep¹

*Address all correspondence to: rok.orel@kclj.si

1 University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia

2 Clinical Nutrition Unit, Institute of Oncology Ljubljana, Ljubljana, Slovenia

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