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Advances in Nutrition of Patients with Inflammatory Bowel Diseases

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Abstract

Inflammatory bowel diseases (IBDs) are multifactorial disorders whose aetiology and pathogenesis have not been fully elucidated. Their occurrence is affected by genetic and environmental factors. Amongst the environmental factors, proper diet seems to be crucial, both in the healthy population and in patients during disease exacerbations and remissions. Depending on their severity, duration and extent of inflammatory lesions, IBD exacerbations result in some dietary deficits. Appropriate supplementation can effectively correct the deficits; in some cases, mainly in CD, nutritional therapy can be equally effective for inducing remissions as pharmacotherapy. Enteral feeding is recommended in each case without important contraindications for its use. Counteracting the caloric, protein and microelement deficiencies is pivotal for inhibition of disease pathogenesis and for enhancement of the anti-inflammatory response of the organism. The present paper is to present simply review and analyse of recent reports regarding nutrition in patients with CD and UC as well as to discuss recommended nutritional management in certain IBD course-associated conditions. Nutritional therapy is a key element of management of IBD patients.

Keywords: Enteral nutrition; Crohn`s disease; Ulcerative colitis; Diet in IBD; Nutrition deficiences in IBD

Introduction

Inflammatory bowel diseases (IBDs) are multifactorial disorders whose aetiology and pathogenesis have not been fully elucidated. Their occurrence is affected by genetic and environmental factors. The environmental factors that can influence the occurrence of the first symptoms and subsequent exacerbations include diet, changes in the intestinal microbiome associated with it, some drugs, particularly contraceptives, tobacco smoking, stress and lack of physical activity. In recent years, a relation between increased IBD incidence rates, perinatal and early childhood infections and infections caused by atypical pathogens has been highlighted. The latest genetic studies have revealed the occurrence of over hundreds loci of genes associated with the risk of Crohn`s disease (CD and ulcerative colitis (UC); nevertheless, the predisposition alone is not sufficient for the disease to develop [1]. Amongst the environmental factors mentioned above, diet seems crucial, both in the healthy population and in patients during disease exacerbations and remissions. Depending on their severity, duration and extent of inflammatory lesions, IBD exacerbations result in various dietary deficits. Appropriate supplementation can effectively correct the deficits. In some cases, mainly in CD, nutritional therapy can be equally effective for inducing remissions as pharmacology. The present paper is to review and analyse recent reports regarding nutrition in patients with CD and UC as well as to discuss recommended nutritional management in certain IBD course-associated conditions. We used several data base: Cochrane library, Scopus, Web of science and Pub-med. As a key words for search we used: ulcerative colitis, Crohn's disease, nutrition, enteral feeding.

Effects of diet on the IBD incidence and course

Study findings regarding the effects of diet on the IBD incidence are contradictory. It seems undeniable that increased incidence rates of IBDs in North America and Western Europe are related to consumption of highly processed food products containing large amounts of trans fats as well as simple sugars and limited intake of fibre, vegetables and fruits [2-6]. Moreover, some studies have demonstrated an inverse correlation between consumption of citrus fruits, fruit and vegetable juices vs. incidence of CD and UC [7,8]. According to the study carried out in Denmark in 118 patients with IBD and in several-hundred controls, high sugar intake significantly increased the risk of IBDs while consumption of large amounts of vegetables had protective effects [9]. To maintain the integrity of the intestinal mucosa, hence the intestinal barrier, it is essential to consume the products rich in fibre. The fibre after fermentation is metabolised by intestinal bacteria to short-chain fatty acids inhibiting the transcription factor involved in the production of pro-inflammatory cytokines [10]. In another study in 168 children, including 53 diagnosed with CD and 27 diagnosed with UC, diets of CD children have been found to contain higher amounts of meat, sugar, fats and lower amounts of vitamins [11]. The EpiCom study conducted on the population of 1560 patients with non-specific inflammatory bowel diseases has revealed that increased intake of sugars and fast food was associated with the earlier first episode of IBD and higher risk of severe course and surgery amongst patients with UC [12].

Patients often associate disease exacerbations with the diet and e.g. avoid vegetables they believe have adverse effects on their health. The New Zealand genes and diet in IBD study has indeed shown polymorphisms of single nucleotides correlated with intolerance of cruciferous vegetables in some patients with CD [13]. Determination of these changes in the population of CD patients could help to

identify the group of individuals in which the vegetable diet would be indicated without increased risks of exacerbations [13]. Furthermore, a correlation between the consumption of hardened fatty acids, e.g. margarines, and granulomatous ileitis [14] and UC [15] has been observed. The observations in the Greenland Eskimo population consuming large amounts of polyunsaturated omega-3 fatty acids from sea fish oil and characterised by low incidence rates of IBDs enabled to formulate the thesis about anti-inflammatory properties of these substances, as opposed to pro-inflammatory properties of omega-6 fatty acids [16,17]. The further studies have confirmed that omega-6 acids are involved in the pathogenesis of IBDs through the metabolic pathway of arachidonic acid, a source of leukotriene B4 showing pro-inflammatory activity. According to Costea et al. [18] carriers of specific variants of genes responsible for metabolism of polyunsaturated fatty acids are at a higher risk of CD when their diets are rich in omega-6 acids and poor in omega-3 acids [18]. The above findings have drawn new attention to the importance of intake of suitable fats in inflammatory diseases, as fats are the main components of cell membranes, of both the gastrointestinal (GI) tract and immune system cells [19].

The IBD incidence shows high geographic differentiation with clearly rising rates in the north regions, both in America and Europe. Many researchers believe that this differentiation is associated with short exposure to sunlight in northern countries, hence vitamin D deficiency. Vitamin D acting through the nuclear receptor is a relevant factor of the signalling pathway responsible for regulation of innate immunity [20]. The Nurses' Health Study has confirmed this theory showing that the risk of UC in women growing up in southern latitudes was lower, as compared to the populations living in northern and mid- latitudes. No such a relation has been found for CD [21]. An animal model of colitis has demonstrated that lack of vitamin D or 1,25(OH)2D3 receptor results in higher susceptibility to GI tract damage [22].

Numerous studies have demonstrated that breast-feeding reduces the risk of CD and UC [23-26]. The study by Bergstrand et al. reveals a relation between reduced risk of CD and longer breast-feeding [25]. Unfortunately, the reports on this relation are conflicting. According to the study carried out in 222 patients with CD diagnosed before the age of 17 years, breast-feeding was a statistically significant risk factor of this disease [27]. Another meta-analysis based on 14 population case control studies has shown that breast-feeding had protective effects on UC incidence; no such a relation was found in the case of CD [28]. Moreover, there are studies demonstrating no effects of breast-feeding on the risk of IBDs [29]. Likely positive effects of breast-feeding result from the changes in bacterial flora of the newborn GI tract. The intestinal contents of children who were breast-fed was found to contain significantly higher numbers of bifidobacteria and statistically significantly lower amounts of anaerobic bacteria. Intestinal microbiota can undergo changes to the age of 2 years and therefore breast-feeding above the standard 6 months can be essential.

Some other studies report negative effects of cow milk consumption on the incidence of non-specific inflammatory bowel diseases. Specific antibodies are detected in the population consuming cow milk, as compared to the control group, whose level correlates with a CD activity index [30].

Despite the publications discussed above, an absolute correlation between diets and IBD etiopathogenesis has not been elucidated. Undeniale changes in the composition and method for processing food in developed countries are factors contributing to morbidity, yet other environmental factors that can affect these processes are not fully known.

Nutritional deficiencies in IBDs

In IBDs, especially in the course of CD involving the small intestine, patients develop various nutritional deficiencies. The degree of nutritional disorders depends on the location of inflammatory lesions, their extent and duration of exacerbation. Compared to UC, CD more frequently leads to protein deficiencies and certain nutritional disorders (avitaminosis, deficits of microelements) [31]. The study in IBD patients indicates that the problem regards 23% of ambulatory patients and even 85% of those requiring hospitalisation [32]. The problem is predominant in CD patients [31,33,34]. One of the nutritional status index of IBD patients is the level of albumins, which correlates with caloric-protein deficiencies and body weight loss. Significant weight losses are observed in 75% of patients hospitalised due to CD exacerbations whereas negative nitrogen balance is found in about 50% of cases [35,36].

The main factors predisposing to nutritional deficiencies are intolerance to multiple food products, abstaining from eating due to therapeutic reasons, increased calorie demands in the course of disease, malabsorption in the substantial fragment of the inflammation-affected intestine or interactions between food and drugs [37-39]. The less common factors include chronic diarrhoea and vomiting, chronic GI bleeding, enteropathy with loss of proteins, mucus and electrolytes, complicated infections, fistulae or impaired absorption of biliary salts in the case of bowel resection [40-44] (Table 1).

Causes of nutritional disorders in IBD patients	
Limited oral intake	Dietary restriction Lack of nutrition due to therapeutic reasons Related to diarrhoea, nausea, vomiting, abdominal pain [45] Changes in taste caused by drugs and vitamins taken and mineral deficiencies [43] Anorexia-like effects of pro-inflammatory cytokines [43]
Loss via the stomach or intestine	Diarrhoea Bloody stools Loss of mucus and microelements Enteropathy with loss of proteins

Increased energy demands	Inflammation Increased basal metabolism Infection complications Conditions after surgery
Metabolic disorders	Increased energy expenditure due to inflammation, fever, sepsis Increased oxidation of fatty acids
Drug interactions	Steroids and calcium re-absorption Steroids and protein catabolism Sulfasalazine and folic acid Methotrexate and folic acid Cholestyramine and fat-soluble vitamins Micro-organisms and vitamin K [46,47] IPP and iron [48]
Low absorption of food	Reduced absorption area due to ileal resection Blind loop syndrome and bacterial overgrowth Poor absorption of bile acids in ileitis or following resection Inflammation of the mucous membrane

Table 1: Causes of nutritional disorders in IBD patients.

Moreover, the pro-inflammatory cytokines (such as TNF- alpha, IL1, IL6), involved in the pathogenesis of IBDs, are responsible for worsened nutritional status due to catabolism-increasing effects. The most common deficiencies of microelements are those regarding iron reserves, vitamin B12 and folic acid manifesting in anaemia detected in laboratory tests. Folic acid deficiencies are observed in over half of IBD patients and most likely result from low-fibre diets, malabsorption or drug interactions, e.g. sulfasalazine or methotrexate. Some drugs exert adverse effects on the nutritional status of IBD patients; for instance, metronidazole can cause reduced intake due to dyspeptic symptoms or metallic taste in the mouth, steroids reduce calcium absorption from the GI tract and increase its loss through kidneys whereas cholestyramine impairs absorption of calcium, fats and vitamins dissolved in fats [32].

The study by Goh et al. has demonstrated that the folic acid deficiency is associated with increased risk of neoplasia in IBDs [31]. According to some other studies, the substance in question exhibits protective properties against the development of dysplasia and carcinogenesis in patients with long-term UC [49,50]. The deficiency of folic acid is also associated with increased risk of thromboembolic incidents in UC and CD via the effects on homocysteine metabolism [51]. Another factor affecting homocysteine metabolism, and indirectly increased risk, is vitamin B12, whose deficiency is detected in about 20-60% of patients with inflammation of the terminal ileum during CD.

Important immunological processes are impaired by zinc and selenium deficiencies. Zinc is essential for wound healing; therefore, its deficiency should be considered in the case of Crohn`s disease complicated by unhealing fistulae [52,53]. Moreover, zinc plays a crucial role in anti-oxidative processes since (being a co-factor of superoxide dismutase) it is involved in cell protection against harmful effects of active oxygen forms. Oxidative stress is positively correlated with the level of pro-inflammatory cytokines. Selenium, vitamins A, C and E also have anti-oxidative properties, positively affecting the limitation of inflammation [54,55].

The information concerning deficiencies of other microelements is sparse; nevertheless, they are likely to be involved in the immune response regulation, depending on their extent, frequency and duration.

The consequences of dietary deficiencies depend on the patient's age the disease develops in and the disease activity. Considering earlier occurrence of CD, as compared to UC, and its frequent development in the small intestine, the risk of clinical manifestations of dietary deficiencies is higher in CD patients. Nutritional deficiencies in children with IBDs often lead to growth inhibition and delayed maturation, which regards about 10% of UC children and about 75% of CD children [40]. Protein deficiencies induce disorders of hormonal and immunological metabolism, resulting in higher risk of infections due to the translocation of intestinal bacteria.

Disorders of bone metabolism are likely to be multifactorial and result from vitamin D deficiency, reduced calcium intake, steroid drugs, insufficient physical activity and impaired absorptive function of the intestinal villi affected [56].

Nutrition as therapeutic management in IBD

Nutritional therapy is a key element of management of IBD patients. Enteral feeding is recommended in each case without absolute contraindications for its use. Counteracting the caloric, protein and microelement deficiencies is pivotal for inhibition of disease pathogenesis resulting from those disorders and for enhancement of the anti-inflammatory response of the organism.

Liquid and semi-liquid preparations are used for enteral feeding, which can be divided into elementary, half-elementary and polymeric. The elementary mixtures contain only amino acids, glucose, fatty acids and microelements, i.e., components that do not require digestion.

Semielementary diets involve administration of mixtures of small peptides, oligosaccharides and medium-chain fatty acids whereas polymeric diets consist of the mixture of proteins, carbohydrates, medium- and long-chain fatty acids, vitamins and trace elements [57]. Nutritional therapy can be oral or through the nasogastric or nasointestinal tube, depending on the patient's condition. Benefits of enteral feeding are dependent on the location of inflammatory lesions, their extent and intensity. According to the guidelines available, total enteral nutrition was most commonly introduced for the period of 6-8 weeks; then the normal diet was gradually included [58]. The preparations applied most frequently, both elementary and polymeric, contained about 1 kcal/ml and only slightly varied in their composition–most commonly, proteins were a source of 14-22% of energy, carbohydrates of 50-82% and fats if up to 35% of calories [59-64].

Gassull et al. [62] compared the efficacy of two nutritional formulae and steroid therapy for induction of remission in the course of CD. Both mixtures differed only in the fatty acids contained predominantly– in the first one, it was oleic acid (monounsaturated fatty acid MUFA) and in the other one linolenic acid (polyunsaturated fatty acid PUFA). The study was discontinued prematurely because only 20% of oleic acid formula patients had remission after 4 weeks. The group treated with linoleic acid formula showed the 52% efficacy; the efficacy in the group administered steroids was found to be 79%. The authors suggest that the effectiveness in inducing remission is significantly affected by the composition of fatty acids in the nutritional formula and hypothesize that n-6 MUFAs are less effective as they are the precursors of pro-inflammatory factors.

Leiper et al. described their randomized trial comparing the efficacy of induction of CD active response to the polymeric diet with high (group 1) or low (group 2) content of long-chain triglycerides. In both groups, the response rate was above 50% and no significant intergroup differences were observed [65]. The study by Gorard et al. compared the efficacy of CD remission in the group of 22 patients receiving the enteral diet for 4 weeks and 20 patients treated with steroids in a dose of 0.75 mg/kg daily for 2 weeks with a subsequent dose reduction. Unfortunately, nine patients of group 1 discontinued treatment due t enteral feeding intolerance. Amongst the remaining patients in both groups, the effectiveness of remission was comparable; however, a statistically significant difference in favour of steroid therapy regarded possible 6-month remission, 0.67 vs. 0.28 [66].

Another study demonstrated comparable efficacy of nutritional therapy and steroid therapy in induction of CD remission in adults (80% vs. 88%) [67].

The available literature indicates that patients with small intestine CD benefit most from enteral nutrition. According to meta-analysis of randomized studies published by Fernandes-Baranes et al, enteral nutrition is equally effective for inducing remission in the case of active CD as steroid therapy [68]. Moreover, nutritional therapy enables to maintain CD remission [69-71] and statistically significantly delays the need for surgical intervention or possible re-intervention [72]. Furthermore, numerous publications revealed that total enteral nutrition was associated with higher mucosal healing [73], changed intestinal microflora [74] and quicker weight gain [75], higher concentration of vitamin D [76], improved bone metabolism [77], increased insulin-like growth factor [78] and better quality of life after treatment [79], as compared to steroid therapy.

The paediatric studies suggest that higher effectiveness of nutritional therapy are observed in children with newly diagnosed CD (80%) in comparison with therapy of exacerbations of long-lasting disease (58%) [75].

Despite the benefits of total nutritional therapy, the management is not univocally recommended in algorithms of IBD treatment instead of pharmacological therapy; it is only advocated as supplementary therapy [80,81]. In many studies, negative effects on the percentage of nutritional therapy efficacy resulted from more frequent abandonment of nutritional mixtures due to unacceptable taste or troublesomeness of long-term nutrition through the intestinal tube. Additionally, some patients on enteral feeding reported abdominal pain, flatulence and symptoms of reflux disease. The review of studies on total enteral nutrition presented by Wall et al. suggests that despite numerous promising reports, there is no evidence demonstrating higher efficacy of his therapy in patients with newly diagnosed CD and casus of ileum location. The authors suggest that the use of oral nutrition with polymeric diets of acceptable taste can markedly improve the percentage of patients following orders and result in higher percentage of induction of CD remission, improved nutritional status and effective control of deficiencies [82].

Most importantly, nutritional therapy has no significant adverse side effects, as opposed to pharmacological methods widely used in IBDs. There are no explicit data regarding the effects of nutritional therapy on CD confined to the large intestine. Moreover, benefits of this kind of therapy in UC have not been explicitly demonstrated. Rare studies on the role of nutrition in UC exacerbations indicate no distinct differences in the impact on the remission index or need of colostomy between enteral and parenteral nutrition in patients treated with steroids [83]. Enteral feeding in UC exacerbations shows anabolic action, is safe and justified when the nutritional status has to be improved and deficiencies corrected.

Enteral feeding mechanism of action

The mechanism of effects of enteral feeding on inhibition of the inflammatory reaction is multifactorial [46]. It is known that one of the elements of IBD pathogenesis is increased permeability of the mucosa, which improves as a result of nutritional therapy used. The available data suggest that the administration of nutritional preparations regulated impaired balance in the composition of intestinal bacterial flora, responsible for activation of improper immune response. The exposure to intestinal antigens from improper intestinal microbiota decreases; most likely, the expression of genes of the intestinal epithelial cells, which affect immune reactions changes [84,85]. The use of elementary mixtures considerably reduces the digestive effort, peristalsis and secretion related to the process of digestion, which beneficially affect the process of recovery [47]. Moreover, the elementary diet can reduce the number of commensal bacteria in the GI tract, which are likely to be involved in the induction of inflammation. The reports on this issue are not explicit; no positive effects of elementary diets were confirmed in scientific studies, which did not demonstrate the differences in therapeutic efficacy of elementary vs. non-elementary diets [86].

The knowledge about negative effects of improper dysbiosis on intestinal epithelial dysfunction, increased stimulation of the immune system and reduced resistance to damaging factors suggests high impact of properly chosen probiotics in the treatment of IBDs [87].

Nutritional therapy with probiotic preparations shows significant effects on maintenance of remission in UC patients and therapeutic benefits in the therapy of pouchitis.

In recent years, numerous studies were devoted to the effects of probiotics in maintenance of remission in IBD patients. They demonstrated the impact of short-chain fatty acids (SCFAs), such as butyrate, propionate and lactate, on the composition of intestinal microbiota. SCFAs are produced due to fermentation of fibres by some intestinal bacteria, e.g. lactobacillus or bifidobacterium and are a relevant substrate nourishing enterocytes and positively affecting on the properties of the intestinal epithelium. The best known prebiotic of proved anti-inflammatory action is butyrate [88,89].

Some reports suggest that the key therapeutic element of enteral nutrition is proper appropriate composition of fats [62,67]. However, there is no consensus as to the recommended composition and proportion of fatty components. It was explicitly demonstrated that dietary supplementation of omega-3 fatty AIDS beneficially affects the maintenance of remission in CD patients; no such a relation was confirmed in the case of UC [90-92]. Despite conflicting data regarding the efficacy of administration of fatty components in enteral nutrition, this kind of management is recommended due to therapeutic potential and lack of adverse side effects.

Analysis of reports on the effects of enteral nutrition on maintenance of remission in patients receiving biological therapy provides interesting information. In one of the studies, 56 patients with remission during infliximab treatment, the therapy was continued in a standard dose. Patients were divided in to the group additionally receiving night and day elementary diet and the group without dietary restrictions. The level of CDAI after the 56-week observations did not show differences, which indicated lack of effects of nutritional therapy on maintenance of remission in patients receiving supportive infliximab therapy [93]. In another study, the 85-week observation of patients receiving infliximab supportive therapy revealed that the additional use of nutritional therapy >600 kcal/24h with elementary and polymeric formula is an independent factor maintaining a stable response to the biological drug [94]. Positive effects of nutritional therapy on maintenance of CD remission in patients subjected to chronic infliximab therapy was described by Hirai et al. The cumulative remission index was significantly higher in the group additionally receiving, compared to the group without nutritional therapy; moreover, multi-variant analysis demonstrated that such management is the only relevant factor preventing the recurrence of disease [95].

Parenteral nutrition of patients with IBDs shows numerous adverse side effects with increased risk of systemic infections; and most importantly is not beneficial for IBD control [96,97]. No positive effects of parenteral nutrition on maintenance of remissions and in its induction were demonstrated in both CD and UC. This way of nutrition is the management of choice in cases with contraindication for enteral feeding, such as short bowel syndrome after extensive resection, megacolon toxicum, increased GI bleeding or CD complicated with difficult healing of fistulas [98,99].

Dietary guidelines in patients with IBD

Diverse diets rich in vegetables, fruits, meat, sea fish, olive oil and cold-pressed linseed and rapeseed oil is essential for nutrition of patients with IBDs.

Moreover, intake of high amounts of fibre is recommended except of patients with significant intestinal constriction, functional diarrhoea disorders, e.g., in concomitant irritable bowel syndrome or patients with highly active IBD exacerbations

In patients diagnosed with lactose intolerance and those with IBD exacerbations, it is recommended to withdraw milk and dairy products. To supplement calcium deficiencies, high-calcium soya products or feta cheese should be consumed.

In order to present frequent deficiencies in IBD patients, calcium (1000 mg/24h) and vitamin D (400-800 IU) should be controlled and supplemented, especially in patients undergoing long-term corticotherapy, whose risk of osteoporosis is higher. Moreover, the levels of iron and folic acid should be monitored as their deficiencies are the most common cause of anaemia; likewise, the level of vitamin B12 should be monitored, particularly in patients after resection of the terminal ileum segment.

It should be remembered that resection of the terminal ileum segment impairs the intestinal hepatic loop of circulation of biliary acids, which are crucial for digestion and absorption of fats and vitamins dissolved in fats (A,D,E,K). Patients with extensive active diseases of the small intestine or after resection of the terminal ileum segment are recommended to reduce the intake of fat and oxalates due to increased risk of renal calculosis [100,101].

Noteworthy, while choosing the nutritional preparations available on the market supporting IBD treatment, the patient's preferences should be considered (frequency of use, time, taste or the administration router in some cases). In patients with highly protein or corresponding to the high caloric demands elementary diets or partially elementary diets, nocturnal nutrition through the nasogastric tube should be considered.

Conclusions

Among the environmental factors affecting the incidence of IBD-proper diet is important both in the healthy population to reduce the risk of incidence of IBD, and also has a significant impact on the disease course and length of remission periods.

In the course of IBD a significant percentage of patients develop nutrition's disorders and relevant dietary deficiency. CD compared to UC leads to a higher protein deficiency and other nutrition's disorders such as deficiency of vitamins A, D, E, iron, vitamin B12, folic acid and trace elements like Zink and potassium.

It is necessary to carefully monitor the patient for early diagnosis of malnutrition and appropriate supplementation.

Enteral nutritional therapies restore impaired nutritional status in the population of IBD patients and positively modulate intestinal immune response.

This management is particularly recommended for children with CD and can prove sufficient to induce remission without corticotherapy.

In patients with CD and severe cases of UC, enteral nutrition is recommended as additional management supporting induction of remission and counteracting adverse effects of drugs [86]. In this group, nutritional therapy can be used to induce remission when corticotherapy is contraindicated [102].

Conflict of Interest

"The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

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