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Influence of environmental factors and diet on inflammatory bowel diseases – a review of the literature

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Abstract

Introduction and objective

Inflammatory bowel disease (IBD), leading to inflammation in the gastrointestinal tract, causes a number of bothersome symptoms that contribute to the deterioration of patients' quality of life both physically and psychologically. Therapy methods based on pharmacotherapy in IBD often remain insufficient in the treatment of these disorders, so other factors affecting the course of IBD are being sought. The purpose of this review is to present risk and prevention factors for the development of inflammatory bowel disease based on diet and environmental factors.

Abbreviated description of the state of knowledge

The review has identified a number of factors that influence IBD. One of these is smoking, which shows a commonly detrimental effect on CD, while it has a protective effect in UC patients.

Antibiotic therapy, by disrupting the composition of the endogenous intestinal microflora, contributes to an increased risk of IBD exacerbations. A review of the literature on surgical interventions does not allow a clear conclusion. Stress and psychiatric disorders increasing the production of pro-inflammatory cytokines, inhibiting the anti-inflammatory action of the vagus nerve increase the risk of IBD exacerbations. A healthy and balanced diet is an important aspect in the treatment of UC and CD. Scientific societies unanimously recognize breastfeeding and its effect on the development of the intestinal microflora as an important protective factor. On the other hand, introducing an elimination diet without a food intolerance confirmed by a blood test is unjustified and harmful.

Summary

Awareness of the risk factors for development and exacerbations in IBD patients is crucial. Further research into the impact of diet and environmental factors may support pharmacological treatment in achieving therapeutic success in patients with inflammatory bowel disease.

Key words: inflammatory bowel diseases, diet, lifestyle, environmental factor, stress

Introduction

Diet and lifestyle are the main environmental factors associated with the onset and course of inflammatory bowel diseases (IBD) [1]. This group includes ulcerative colitis (UC) and Crohn's disease (CD). These diseases have similar symptoms and lead to digestive disorders and inflammation in the gastrointestinal tract. The specific cause of their occurrence is still unknown. It has been hypothesized that these diseases may develop, in individuals with a genetic predisposition, who have adverse environmental factors, an altered intestinal microbiome and a dysregulated immune response [2,3]. Ulcerative colitis causes inflammation and ulceration of solely the epithelial layer and, to a lesser extent, the submucosal layer of the large intestine. The disease localizes in the rectum or colon, or in more severe cases in both locations [4]. Crohn's disease distinguishes itself from ulcerative colitis by its ability to localise throughout the entire gastrointestinal tract, from the mouth to the rectum. It involves all layers of the digestive tract, leading to its destruction. Characteristic of the disease is the presence of fistulas, or abnormal

connections between loops of intestine or other organs [5]. Both of these diseases have a significant impact on the quality of life, mental health and physical performance of patients [6].

Objective

The aim of this review is to present risk factors and a variety of ways to prevent the development of inflammatory bowel diseases based on diet and environmental factors.

State of knowledge

Environmental factors and IBD

Recent studies confirm the important role of environmental factors in the pathogenesis and epidemiology of IBD. Current epidemiological data have shown that the incidence of IBD is increasing in developing countries, including South America, Asia, Africa and Eastern Europe [7,8]. The change in epidemiological patterns in populations where IBD was previously not common again raises the question of important environmental factors involved in the development of these chronic inflammatory diseases.

Smoking is one of the most studied triggers of IBD. Clinically, smoking has been shown to be detrimental in patients with CD, while it has a protective effect in patients with UC [9]. In Crohn's Disease, it is often associated with early disease onset and more aggressive progression, with an additional increase in the incidence of strictures and fistulas and an enhanced probability of a future need for surgical intervention. A 56-85% increase in Crohn's disease exacerbations has been observed in smokers. Smoking is associated with increased corticosteroid use and addiction. Smokers also achieve higher nucleotide 6-thioguanine levels compared to non-smokers. Smoking patients with CD, have intestinal dysbiosis characterized by a higher Bacteroides: Prevotella ratio compared to non-smokers. Studies suggest that intestine microbiota dysbiosis may be a reason why cigarette smoke may increase the risk of developing CD [10]. Chronic smoke exposure may also negatively affect the intestinal microflora by altering the mucus profile and local immune environment, through increased secretion of two major mucins of the ileum: Muc2 and Muc3, and increased expression on the cell surface of the anti-adhesive Muc4. Furthermore, particulate matter

ingested in cigarette smoke disrupts intestinal function, causing changes in mucosal microcirculation and mucosal repair processes [11].

It has also been shown that at the cellular level, cigarette smoke affects dendritic cell phenotypes by altering molecular and receptor functions. Carbon monoxide prevents the maturation of dendritic cells and reduces the production of pro-inflammatory cytokines and proliferation of effector T cells, while it stimulates the secretion of the anti-inflammatory cytokine IL-10, which may explain the beneficial effects in the treatment of UC [12].

Another environmental factor contributing to the increased incidence of IBD is the use of drugs, especially antibiotics [13]. This correlation is usually attributed to changes in the intestine microbiome following antibiotic use in the early stages of life, when the microflora has a crucial role in shaping immune cell development [14]. Non-steroidal anti-inflammatory drugs, contraceptives and statins are other examples of drugs that have been connected to a doubled risk of Crohn's Disease and ulcerative colitis [15]. A major role in the epidemiology of inflammatory bowel diseases is played by the "hygiene hypothesis," that is, early life events such as mode of delivery, breastfeeding, exposure to pets and infections. These are the factors associated with IBD, mainly due to their impact on the development and composition of the intestinal microflora. Exposure to antibiotics due to infections in the first year of life has been shown to increase the risk of IBD in the future. Breastfeeding, on the other hand, is a particular protective factor for IBD. Moreover, lower environmental hygiene, which includes early contact with farm animals or pets, also has a protective effect on IBD [16,17].

Urban living is a risk factor for the development of Crohn's disease and ulcerative colitis, which may be due to easier access to antibiotics in childhood, or greater exposure to chronic stress. Moreover, a Canadian study found a protective effect of living in a rural area on the risk of IBD in childhood. These findings may account for the beneficial effects of the village environment from an early age and provide support for the "hygiene hypothesis" [18,19].

Interestingly, surgical interventions have also been shown to have an impact on the development of IBD. This finding is supported by a study by Deng and Wu, in which appendectomy had a protective effect against ulcerative colitis [20]. On the other hand, an increased risk of developing Crohn's disease was observed after this surgery [21]. The relationship between appendectomy and CD is still not conclusive. Studies reveal a later diagnosis of CD in people who have previously undergone appendectomy surgery. Another inspiring finding is a meta-analysis of 17 studies which showed that there was an increased risk of developing CD after tonsillectomy and no association with the development of UC. The tonsils, appendix and Peyer's tufts are rich in mucosa-associated lymphoid tissue. Its potential contribution to the development of inflammatory bowel diseases is acknowledged. Other studies show that the risks associated with appendectomy or tonsillectomy may also be associated with the use of antibiotics to treat these conditions [22].

Another environmental factor that is often considered in the epidemiology of IBD is stress and psychological disorders. It has been shown that depression or anxiety disorders can promote the recurrence of inflammatory bowel diseases and worsen the clinical condition of patients. Mental stress affects intestinal permeability, peristalsis, sensitivity and secretion, as well as the composition of the intestinal microbiota [23]. Mental stress also inhibits the anti-inflammatory effects of the vagus nerve, as it reduces nerve tension and accelerates the production of inflammatory cytokines [24]. In both UC and CD patients, lower vagus nerve activity is associated with systemic inflammatory symptoms, especially excessive production of TNF-α and C-reactive protein (CRP). The intestine is richly innervated by the so-called enteric nervous system (ENS). Stress-induced activation of the sympathetic nervous system stimulates the enteric ENS and increases the density of nerve fibers and the number of cholinergic neurons in the intestinal mucosa, leading to greater permeability of the intestinal epithelium. Clinical studies have shown that lesions in patients with CD and UC are characterized by a greater number of submucosal nerve plexuses and increased epithelial permeability [25]. The impact of stress on the enteric nervous system (ENS) through hypothalamic-pituitary-adrenal axis (HPA axis), autonomic nervous system (ANS) and microbiota brain-gut axis is illustrated in Figure 1 [23-25].

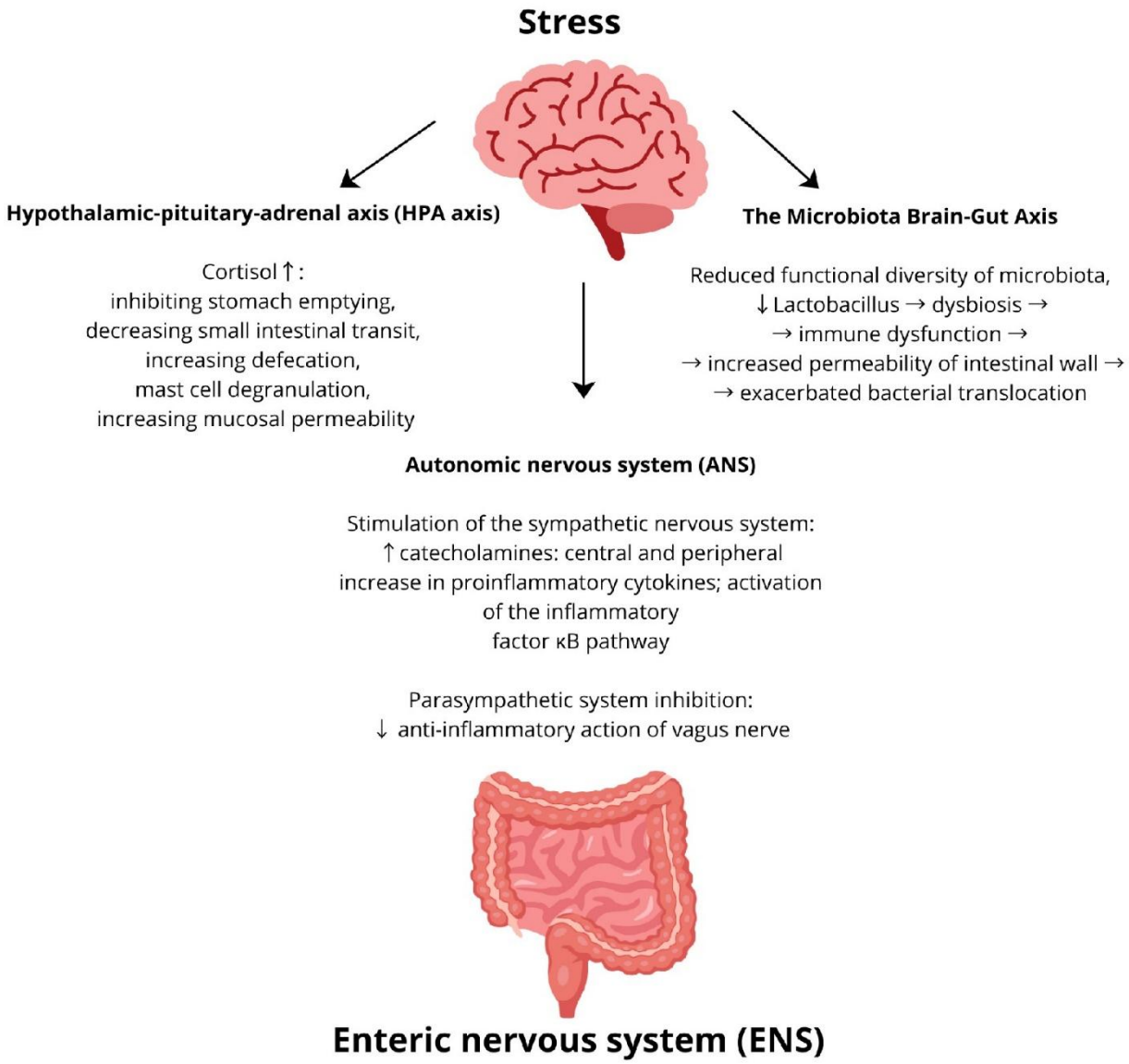

Figure 1. Effects of stress on the enteric nervous system.

Source: author's compilation based on the studies [23-25].

Nutritional factors in the etiology of IBD

A healthy and balanced diet plays a key role in the treatment of many inflammatory diseases. Dietary changes can be helpful in relieving symptoms such as abdominal pain, bloating or diarrhea and reducing complications of inflammatory bowel diseases [26]. The impact of diet on IBD is still widely debated in the literature because there are no clear dietary guidelines. This lack of accurate information forces patients to seek information from various, often false, sources. Ultimately, it

increases the risk of self-imposed dietary restrictions, which can have serious negative consequences for patients' health. Eating habits in IBD patients may also be based on personal experiences, which often lead them to avoid certain foods or food groups in order to self-medicate their disease [27].

As it turns out, diet has an important role in the pathogenesis of IBD from an early age. Breastfeeding is a very important protective factor. The formation of the microbiome in childhood and its impact on the development of the immune system is extremely important due to its potentially protective nature on the development of inflammatory bowel diseases [28]. One study showed that intestine microbiome stability is achieved as early as 31 months of a child's life [29]. The early microbial structure of the gastrointestinal tract, favored by breastfeeding, protects against the development of both forms of IBD. Reductions in the risk of both UC and CD were noted with increasing duration of breastfeeding. A particular protective value is achieved if breastfeeding lasted longer than 12 months. The individual odds ratio (OR) values according to feeding time are summarized in Figure 2 and Figure 3. Significantly for CD and UC, a statistically significant OR value occurs between breastfeeding for 12 months and breastfeeding for 3 or 6 months. There was no statistically significant relationship between feeding 3 and 6 months [30].

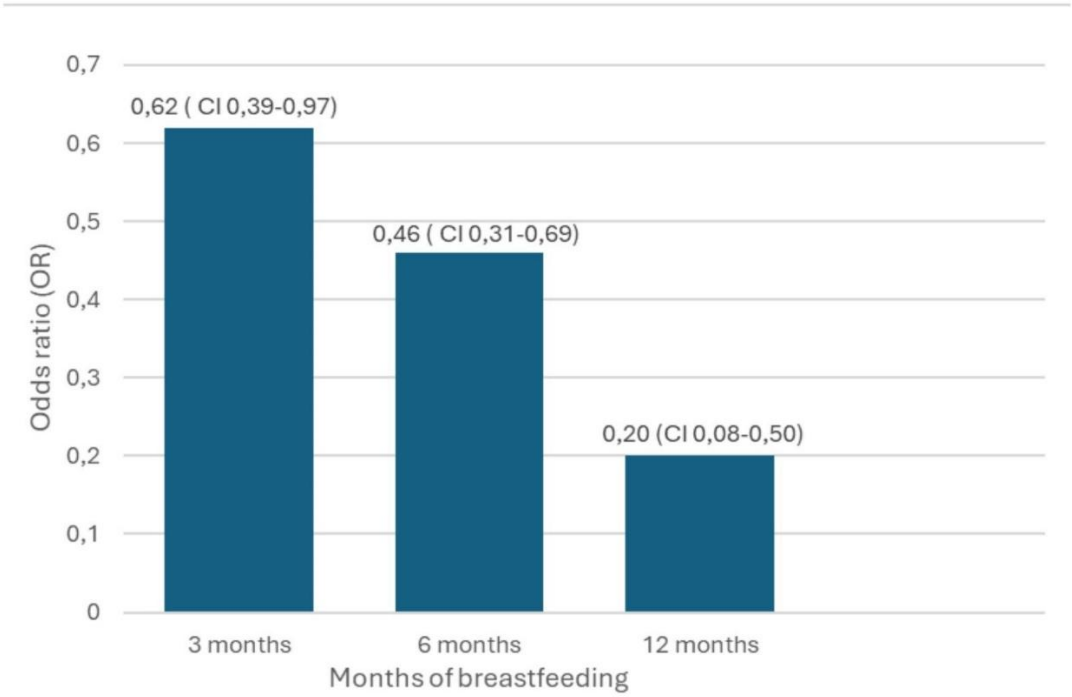

Figure 2: Odds ratios of Crohn's disease (CD) risk associated with breastfeeding at 3 months, 6 months and 12 months.

Source: author's compilation based on the study by Luyi Xu et al [30].

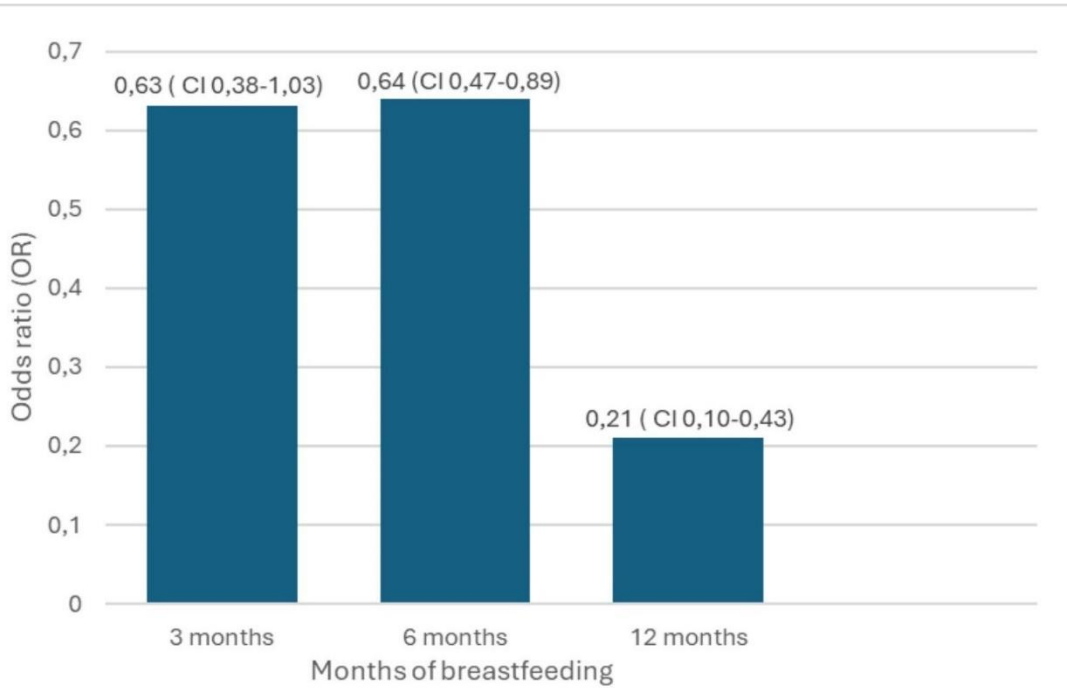

Figure 3: Odds ratios of ulcerative colitis (UC) risk associated with breastfeeding for 3 months, 6 months and 12 months.
Source: author's compilation based on the study by Luyi Xu et al [30].

There is a perception among patients that dairy products negatively affect the stressed gastrointestinal tract. Eliminating lactose from the diet is a form of nutritional management often indicated in studies among IBD patients [31,32]. This has proven controversial, as no significantly increased risk of lactose intolerance has been found in IBD patients compared to the general population. However, a study by Eadal et al. found a prevalence of lactose intolerance in 70% of IBD patients, which was confirmed by hydrogen test and genetic testing, as well as clinical symptoms reported by patients [33]. In contrast, in a study by Jasielska et al. the prevalence of lactose intolerance in children with CD and UC was 23.2% and 22.6%, respectively, and did not differ significantly between sick and healthy subjects [34]. Similar data were obtained in a study by Büning et al. in which the prevalence of lactose intolerance did not differ significantly between healthy subjects, IBD patients and their relatives [35].

According to the latest recommendations of the European Crohn's and Colitis Organization (ECCO) and the European Society for Clinical Nutrition and Metabolism (ESPEN), the implementation of an elimination diet in IBD patients without food intolerance confirmed by blood testing is

unjustified and harmful [36]. Elimination of dairy products is associated with a high risk of calcium and vitamin D deficiencies, which can lead to bone demineralization and, in extreme cases, malnutrition, including protein malnutrition. This clinical condition of patients makes pharmacotherapy much more difficult and worsens the prognosis. Avoidance of elimination diets is particularly important in patients with IBD who have developed osteopenia and osteoporosis as a consequence of recurrent inflammation and steroid therapy [37].

Another diet worth mentioning is the gluten-free diet. This diet is indicated for celiac disease, Duhring's disease and wheat allergy. A gluten-free diet is not recommended for IBD patients. However, studies have shown that it is used by patients to relieve symptoms, despite the lack of objective indications. As many as 28% of IBD patients reported avoiding gluten in the past. There have been several studies showing subjective symptom improvement and reduced relapse rates on a gluten-free diet in IBD patients without a concurrent diagnosis of celiac disease. However, no objective improvement in clinical parameters was found [38].

Many approaches have been made to relate the incidence of IBD to an excess or deficiency of various dietary components. There is an evidence that a significant intake of saturated fat and monosaccharides and a low intake of fiber are associated with an increased risk of developing CD [39]. Retrospective studies in patients with CD have shown a correlation between increased intake of monosaccharides and the onset of malaise [40]. Russel et al. also highlighted drinks such as cola, chocolate, which increase the incidence of IBD and exacerbate symptoms. [41]. Their observations were confirmed by Sakamoto et al. who showed a negative effect of sweets and artificial sweeteners on the risk of developing both UC and CD [42].

High-fat diets, especially those rich in cholesterol and animal fats, may also increase the incidence of IBD [39]. Ananthakrishnan et al. confirmed the effect of increased intake of trans fatty acids on the risk of developing UC [43]. An association between increased linoleic acid (an omega-6 polyunsaturated fatty acid) and a higher incidence of ulcerative colitis has been demonstrated. This fatty acid is a precursor of arachidonic acid (AA), the metabolites of which have been shown to have pro-inflammatory properties, with potential effects on the development of IBD [39]. In contrast, based on a study involving 25639 participants who kept a 7-day food diary, John et al. demonstrated a protective effect of omega-3 unsaturated fatty acid intake on the incidence of ulcerative colitis. In particular, dietary docosahexaenoic acid intake had a beneficial effect [44].

The next important element of a healthy and balanced diet is fiber. According to Ananthakrishnan et al. a diet rich in fiber at 24.3 g/d can reduce the risk of developing CD by up to 40%. Particular attention should be paid to fiber from fruits. However, the authors observed no protective effect against the development of UC [43]. In a study involving 130 subjects under the age of 30 also confirmed the role of dietary fiber intake in preventing Crohn's disease [45].

Considering that meat is a common part of everyone's diet, correlations are also being sought between its consumption and its effect on IBD. There is an evidence that red meat consumption has pro-inflammatory properties. This may be due to the way it is cooked, the simultaneous presence of saturated fats and their harmful effects [46]. Meat-derived protein is fermented by the intestinal microflora, which produces branched-chain amino acids (BCAAs), as well as potentially toxic substances such as ammonia, amines, hydrogen sulfide and nitrogenous compounds. Some of these fermentation products can potentially damage DNA and promote genetic instability. This effect has been demonstrated in healthy individuals consuming red meat compared to a vegetarian diet. However, there is insufficient evidence to show what effect it has on inflammatory bowel diseases [47].

Diet during periods of disease exacerbations

One of the main dietary recommendations during disease exacerbation in patients with IBD, diarrhea and abdominal pain is low fiber intake. However, this does not apply to patients with ulcerative colitis and rectal-only involvement, who may experience constipation. Such patients are advised to eat a diet rich in fiber, as recommended by the World Gastroenterology Organization [39]. According to the recommendations of the European Crohn's and Colitis Organization (ECCO), pediatric patients with mild-to-moderate UC exacerbation are recommended a normal diet. Patients with inadequate nutrient supply can be started on enteral nutrition (EEN) with liquid formulas containing all essential nutrients [48]. A review of studies on the use of EEN in children showed that its effectiveness in achieving remission is comparable to of the glucocorticosteroid therapy [49]. EEN has been shown to promote gastrointestinal mucosal healing in children and adolescents with CD. It is important to gradually introduce a normal diet after 8 weeks of EEN feeding. The introduction of such a diet should last about 7-10 days, with one meal introduced every 3-4 days [50]. Currently, there is no high-quality evidence demonstrating the efficacy of a specific diet in the

treatment of the active form of IBD in adults. At this time, specific dietary treatment in adults cannot be recommended as an alternative to the pharmacological treatment [39].

Summary

Awareness of the risk factors for development and exacerbations in IBD patients is crucial. It allows to support drug treatment and achieve therapeutic success in IBD patients. Although research on diet and IBD has grown significantly over the past decade, much of it remains a mystery. Some communities support therapeutic diets, however they should not be universally recommended. In order to develop standards for the treatment of IBD, future research needs to expand the clinical applicability of diets, as well as provide a better understanding of the mechanism of the dietary action. Combining immunology and microbiology, by evaluating specific immune cell profiles and profiles of cytokines and chemokines, growth and nutritional mediators, would provide further insight into the mechanisms in which diet and environment affects IBD. Further research and including them into the clinical practice could change the future of IBD patients.

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