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GENETIC AND EPIGENETIC FACTORS IN THE GENESIS OF INFLAMMATORY BOWEL DISEASES

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Abstract. Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by chronic inflammation in the gastrointestinal tract. The diseases have a multifactorial etiology, including genetic predisposition, gut microbiota, environmental factors, diet, lifestyle, and socioeconomic status. There is a steady increase in IBD throughout the world, especially in Scandinavia, North America, and Canada, Israel. The contribution of diet to the development and treatment of IBD is enormous. In 2020, the European Society for Enteral and Parenteral Nutrition (ESPEN) published recommendations on dietary management for IBD and provided information on the impact of food on the risk of developing diseases. It has been shown that the use of dairy products may have a predominantly protective effect in the etiology of CD and UC, although a clear dose-response relationship has not been established; Gluten is capable of triggering innate and adaptive immune responses responsible for intestinal inflammation. In addition, there are reports that point to celiac disease as a potential risk factor for IBD. Evidence is presented that the microbiota and vitamin D play an important role in stimulating and regulating the immune system. In turn, intestinal dysbiosis observed in patients with IBD may be either a cause of local intestinal inflammation or potentially one of the factors leading to chronic inflammation in IBD, as well as vitamin D deficiency.

Keywords*: inflammatory bowel diseases, Crohn's disease, ulcerative colitis, genetics, genotype, dairy products, gluten, celiac disease, microbiota, vitamin D, vitamin D receptor*

ГЕНЕТИЧЕСКИЕ И ЭПИГЕНЕТИЧЕСКИЕ ФАКТОРЫ В ГЕНЕЗЕ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА

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Резюме. Воспалительные заболевания кишечника (ВЗК) объединяют язвенный колит и болезнь Крона, которые характеризуются хроническим воспалением в гастроинтестинальном тракте. Заболевания имеют многофакторную этиологию, включая генетическую предрасположенность, микробиоту кишечника, факторы окружающей среды, диету, образ жизни и социально-экономический статус. Во всем мире наблюдается неуклонный рост ВЗК, особенно в странах Скандинавии, Северной Америке, Канаде, Израиле. Вклад диеты в развитие и лечение ВЗК огромен. В 2020 году Европейское общество парентерального и энтерального питания (ESPEN — European Society of Parenteral and Enteral Nutrition) опубликовало рекомендации по

диетотерапии при данной патологии и представило информацию о влиянии еды на риск развития данных заболеваний. Показано, что использование молочных продуктов может иметь преимущественно защитный эффект в этиологии как болезни Крона, так и язвенного колита. Хотя четкой зависимости «доза–реакция» не установлено, глютен способен запускать врожденный и адаптивный иммунный ответ, ответственный за воспаление кишечника. Кроме этого, имеются сообщения, которые указывают на целиакию как на потенциальный фактор риска ВЗК. Представлены доказательства того, что микробиота и витамин D играют важную роль в стимуляции и регуляции иммунной системы. В свою очередь, дисбиоз кишечника может быть либо причиной локального воспаления кишечника, либо одним из потенциальных факторов, приводящих к хроническому воспалению, так же как и дефицит витамина D.

Ключевые слова: *воспалительные заболевания кишечника, болезнь Крона, язвенный колит, генетика, генотип, молочные продукты, глютен, целиакия, микробиота, витамин D, рецептор витамина D*

INTRODUCTION

Inflammatory bowel disease (IBD) unites two main clinical entities: ulcerative colitis and Crohn's disease, which are characterized by chronic inflammation in the gastrointestinal tract [1]. The diseases have a multifactorial etiology, including genetic predisposition, gut microbiota, environmental factors, diet, lifestyle and socioeconomic status.

In high-income countries, the epidemiology of IBD is associated with modernization and Western lifestyle (consumption of mostly refined foods rich in saturated fats and low consumption of vegetables, fruits). The growth of morbidity in developing countries is predetermined by rapid urbanization, industrialization, increasing levels of anxiety, as well as westernization of the population, dietary changes (primarily, an active consumption of gluten-containing products) [2]. In addition, the "Western type of nutrition" is characterized by excessive consumption of animal protein, saturated fats, salt, alcohol with a simultaneous decrease in vegetables and fruits in the diet.

There are significant differences in the epidemiology of IBD worldwide. They are maximally frequent in Scandinavian countries, North America, Canada, Israel. Thus, the annual increase in morbidity in Europe per 100,000 citizens is: for ulcerative colitis — 5–20 cases, for Crohn's disease — 5–10 cases with a clear upward trend. The diseases predominantly affect young people, with an average age of 20–40 years, although they can debut at any age. Currently, in some countries there is a tendency to increase the prevalence of ulcerative colitis in the older age group (the second peak of morbidity occurs after 60 years), and Crohn's disease — in childhood. Men and women have approximately the same morbidity [3].

In the Russian Federation, the incidence of IBD is poorly studied. Large-scale epidemiologic studies conducted in Russia indicate that the prevalence of this pathology corresponds to the average figures for Central Europe. Unfortunately, unlike most European countries, in the Russian Federation, severe, complicated forms of disease with a high percentage of mortality predominate. Scientists consider late diagnosis to be one of the reasons for this unfavorable situation. On average, from the onset of inflammatory process in the gastrointestinal tract to diagnosis it takes from 2 to 6 years [4].

In addition, a number of comorbid pathologies contribute to the negative course of diseases, as patients often suffer from protein-energy deficiency, sarcopenia and deficiency of essential micronutrients (vitamins, vitamin-like compounds, micro- and macronutrients). This is due to the fact that against the background of chronic inflammation, some patients are afraid to eat in order not to cause an exacerbation and (or) not to intensify the already existing symptoms of digestive discomfort. Other patients suffer from different variants of food intolerance, also with the development of dyspeptic and painful symptoms. For both the former and the latter, it is significantly limit their dietary intake of certain food groups.

In children, malnutrition leads to disorders of puberty, connective tissue synthesis and growth retardation. For example, growth retardation at the diagnosis of Crohn's disease and ulcerative colitis has been reported in 10–56% and 3–10% of children, respectively [5].

Malnutrition can manifest as overweight, obesity and even the development of sarcopenia in obesity. According to a systematic review including 783 children with IBD, low body mass index (BMI) (nutritional deficiencies of varying severity) was observed in Crohn's disease in 22–24% of cases. In ulcerative colitis it was observed in 7–9% of cases. BMI corresponding to overweight and obesity was found in 10% and 20–30% of children, respectively [6].

Another very important aspect that aggravates the course of IBD diseases and contributes to the negative outcome is the imbalance in the consortium of microorganisms with perverted immune response [3].

Thus, unbalanced and insufficient nutrition both in terms of basic nutrients and energy and micronutrients alters the homeostasis of the organism and causes dysbiotic state, microelementosis, hypovitaminosis and inflammatory reactions. All of this conditions have a negative impact on the processes of DNA methylation, acetylation and non-coding RNA (ncRNA), contributing to the formation of IBD in genetically predisposed individuals [7].

GENETIC FACTORS IN THE FORMATION OF INFLAMMATORY BOWEL DISEASE

Genome-wide association studies (GWAS) have identified more than 240 genetic loci associated with IBD in humans. The polygenic nature of inheritance has been shown. HLA genes *B40, DR3, DR5, DQ2, DR1*3, CV4* play a certain role in this. The polymorphism *Ala893* — multidrug resistance gene *(MDR1)* and mutation of *IBD5 and CARD15 (NOD2)* genes on chromosome 16 were revealed.

NOD2 protein takes part in the formation of the epithelial protective barrier. Mutation of the corresponding gene leads to a decrease in the synthesis of defensins by Paneth cells and impaired intestinal protective function with penetration of intestinal bacteria into the mucosal cells and the formation of inflammation.

Mutations of the *CARD15 (NOD2)* gene are more common in patients with Crohn's disease and are associated with the development of terminal ileitis complicated by stenosis. There are data on the predominant role of the *HLA B40* gene in the ontogenesis of the disease in elderly people and *HLA DR5* and *CV4* genes in young patients [8].

The majority of IBD genetic associations were obtained in a study of individuals of European (EUR) origins. The sample of the East Asian population (EAS) for determining genetic mutations has a much smaller size [9].

A huge contribution to the study of the genetic architecture associated with human IBD belongs to a group of scientists headed by Z. Liu (2023) who identified 16 new genetic loci in the ancestors of the East Asian population (China, Korea, and Japan) and determined the variance (diversity of traits in the population) of 81 genetic loci in the ancestors of Asian and European origin.

The identified phylogenetic variance was mainly explained by higher minor allele frequencies (MAFs) in Asians rather than equal effect sizes [10]. In addition, researchers found comparable factor inheritability based on single nucleotide polymorphism among European and Asian individuals of previous generations. It is indicating that the magnitude of genetic contribution to disease is almost identical in both populations and that many IBD genetic loci are identical except for some such as tumor necrosis factor 15 (TNF15), colony stimulating factor 2 receptor subunit beta(CSF-β 2R) and IL-23 receptors [11].

Because the variance explained by IBD loci differs by great-grandparent (ancestral) territory, the ability to profile genes and predict risk for Crohn's disease and ulcerative colitis in humans also varies widely. Z. Liu et al. (2023) evaluated this ability using polygenic risk score (PRS) and observed that PRS trained in the EUR population has lower accuracy in the EAS population. The scientists believe that their discovery will allow a better understanding of the genesis of IBD and provide a personalized approach to the therapy [10, 11].

EPIGENETIC FACTORS IN THE ONTOGENESIS OF INFLAMMATORY BOWEL DISEASE

Diet

In both children and adults with IBD, certain dietary interventions have been shown to improve clinical symptoms and reduce the inflammatory burden. However, it is not clear how food and individual food components are involved in the pathogenesis of intestinal damage in IBD. Assessing the effects of diet on disease course is complex because, regardless of the dietary pattern adopted, each diet is based on the consumption of many different food groups that influence each other.

A study conducted in Ireland demonstrated that IBD patients resorted to dietary restrictions in the hope of preventing relapse in 85% of cases, including: avoiding fatty foods in 68%, spicy foods in 64%, and raw vegetables or fruits in 58%. In turn, eating a low-fiber food during relapse reduced the symptoms of the disease in 74% of patients [12].

In other words, it should be assumed that some components of a particular product have a proinflammatory potential and can change the vector of immune response towards mucosal inflammation, characteristic of IBD, and at the same time distort the motor function of the intestine. For example, restriction of foods with high levels of dietary fiber in the diet is accompanied by a decrease in bacterial fermentation and gas formation and contributes to digestive comfort [13].

Although the exact mechanism of the effect of "Western diet" on the body is unknown, the effect of some nutrients on the genesis of IBD has been well studied. For example, the effect of saturated fat on toll-like receptors type 2 and 4 (TLR-2 and TLR-4), which are located on immune cells in the intestine and are responsible for signaling from bacteria. Thus, consumption of fried foods with an abundance of saturated fats induces TLR and causes expansion of inflammation in the epithelium of the digestive tube. In contrast, polyunsaturated fatty acids (PUFAs) reduce TLR expression and have the opposite effect.

A number of amino acids found in the products, such as arginine and glutamine, stabilize the intestinal barrier function and increase the synthesis of mucin, which has a protective effect against the intestinal mucosa.

Fatty and sweet foods disrupt the structure of the gut microbiome, increasing intestinal permeability and enhancing the systemic inflammatory process. In turn, the use of prebiotic foods proliferates the indigenous microbiota, which increases levels of short-chain fatty acids, particularly butyrate (butyric acid), in the GI tract. This acid stabilizes the intestinal barrier by regulating the permeability of the colonic mucosa, inhibits oxidative stress, exerts anti-inflammatory effects and carries out prevention of colorectal carcinogenesis [14]. At the same time, abnormal production of butyrate by the microbiome is recognized as the cause of higher expression of the non-functional form of FOXP3, which is associated with an increased risk of autoimmunity [15].

In 2020, the European Society of Parenteral and Enteral Nutrition (ESPEN) published recommendations on dietary therapy for IBD and provided information on the influence of food on the risk of disease development:

- the threat is reduced with a diet rich in fruits and vegetables, omega-3 fatty acids with restriction of omega-6 fatty acids;
- the risk of Crohn's disease, but not ulcerative colitis, is lower with a diet high in fruit and dietary fiber (more than 22 g/day).

This paper also indicates that breastfeeding should be prolonged to at least 6 months, as randomized clinical trials and meta-analyses have shown that this reduces the likelihood of IBD later in life [16, 17].

The journal Gastroenterology (2020) published an analysis of a large cohort of patients (166,903 women and 41,931 men) who were followed-up prospectively for 25–30 years. For each patient, an empirical dietary inflammatory pattern index (EDIP) was determined from a nutritional questionnaire, which is calculated based on the effect of each type of food on the concentration of inflammatory markers. According to the data obtained from the questionnaires, it was found that individuals who developed Crohn's disease were more likely to use foods with a high inflammation index in their diet. No such correlation was found in patients with ulcerative colitis [18].

The construction and validation of the nutrition model recorded a strong correlation between the empirical inflammatory index and three inflammatory markers determined in blood plasma: IL-6, C-reactive protein (CRP) and TNFaR2, as well as adiponectin and the overall assessment of inflammatory markers [18, 19].

Thus, the current level of knowledge allows us to consider that diet is not only a risk factor for IBD because of its role in the induction of intestinal dysbiosis and aberrant mucosal immune response in genetically predisposed people, but also a potential tool in the treatment of that disease [20, 21].

Dairy products

Both molecular and clinical studies demonstrate that components of dairy products have an inverse relationship with sluggish inflammation and affect key cytokines such as tumor necrosis factor alpha (TNFα) [22]. It has been observed that saturated fats in milk induce inflammatory processes through cytokine gene expression and composition of lactic acid bacteria in the gut [23]. A recent study in mice demonstrated that milk triglyceride consumption alters the composition of bile acids and the microbial community with an inversion of inflammation, i.e., the development of colitis [24].

In an experimental study conducted under the supervision of C. Garcia (2022) studied the role

that milk polar lipids (MFGM) — phospholipids (PLs) and sphingolipids (SLs) — have on colitis activity induced by 1% dextran sulfate sodium solution, colonic transcriptome and gut microbiome. It was found that saplementation of diets high in milk polar lipids had a protective effect. Diets low in milk polar lipids had a dual effect. During the period of colitis exacerbation, polar lipids weaken the disease activity. During the recovery period they cause an increase in disease symptoms and inflammation [25].

Thus, polar lipids in milk should be considered as a nutritional matrix factor that can directly provide health benefits and influence the actions of other dietary fats [25, 26].

A group of authors led by S. Talebi (2023) presented a meta-analysis on the association between different sources of dietary protein (general and animal protein) and the incidence of IBD in the population, which showed that higher consumption of dairy products has a protective effect on the risk of IBD formation. Although the researchers did not observe an association between different sources of animal protein and disease risk, a dose-effect analysis found that a 100 g daily increase in meat in the diet was associated with a 38% increase in IBD risk. Moreover, a positive linear correlation was found between total meat consumption and the likelihood of IBD (Pnonlinearity=0.522, Pdose-response=0.005) [27].

Several retrospective 'case-control" studies have reported either no or a small inverse association between dairy products and IBD risk [28, 29].

Recently, the GBD (Global Burden of Disease) staff published data on the prevalence of IBD in each country and noted that Switzerland, a country famous for cheese production and consumption, has a low incidence of IBD, while the UK and the USA, where the population eats relatively little cheese, have a high incidence of the disease. Thus, it has been shown that utilization of milk and/or dairy products (cheese or yogurt) has a negative correlation with the epidemiology of IBD at the national level in Western countries [30].

A large European prospective cohort study involving 401,326 participants noted a correlation between the use of dairy products (milk, yogurt and cheese) prior to diagnosis and the subsequent development of Crohn's disease and ulcerative colitis. When participants were recruited, their dairy product absorption was determined using validated food frequency questionnaires. The results of this study demonstrate that milk consumption may have a predominantly protective effect in the etiology of these diseases, although no clear dose-response relationship has been established [31].

Somewhat different information is presented in the work of K.Y. Tsai et al. (2023). The authors evaluated the effect of dairy products on the course of ulcerative colitis in patients with pre-existing disease and diagnosed for the first time disease. The authors' conclusions suggest that restricting the dairy diet first and then eliminating trigger factors (medicinal herbs/Chinese tonic products, nutritional supplements, psychological problems, non-dietary factors, namely smoking cessation, cosmetic products and stopping medications by patients themselves in case of disease recurrence) will help to improve disease control and reduce the prescription of medications to patients with ulcerative colitis in daily clinical practice [32].

In a multicenter cross-sectional study involving 12 gastroenterology centers from four countries, scientists needed to determine whether it was really necessary to deprive patients with IBD of dairy product consumption. The study included 872 patients with IBD, 1016 cases without it. In all respondents in comparison, during 6 months, symptoms from the digestive system after consumption of dairy products were evaluated. Based on the material obtained, the authors concluded that there is no convincing data on the negative effect of dairy products on the course of inflammation in the intestine, and, accordingly, dairy products should not be excluded from the diet of IBD patients [33].

Gluten

Gluten is a protein composed of gliadins and glutenins found in most cereals such as barley, wheat and rye [34, 35]. In recent decades, an increasing number of adverse reactions after gluten consumption have been reported in the literature, categorized as IgE-mediated wheat allergy, celiac disease and non-celiac gluten sensitivity (NCGS) [2, 35].

There is a growing number of studies proving that gluten can trigger an innate and adaptive immune reaction responsible for intestinal inflammation. Together with other dietary elements, gluten may contribute to the development of IBD, functional gastrointestinal disorders (FGID) and exacerbation of symptoms in these pathologies. Although the exact role of gluten in the genesis of these conditions remains unclear, at least 50 dif-

ferent gliadin epitopes have been identified that play immunomodulatory and cytotoxic roles, as well as determine intestinal permeability through reorganization of actin filaments and modified expression of connective complex proteins such as zonulin [36]. Some of these epitopes stimulate a pro-inflammatory innate immune response, while others activate specific T cells. K. Ziegler et al. (2019) that amylase and trypsin inhibitors found in cereals containing gluten have the ability to activate TLRs, thereby stimulating the release of inflammatory cytokines and inducing a T-cell immune response [37]. In addition, gliadin induces an inflammatory response by synthesizing a variety of pro-inflammatory cytokines (IL-6, IL-8, IL-13 and INF-1, IL-23, IL-1β and TNFα) [36].

More than half of IBD patients believe that their symptoms are aggravated by certain foods, particularly gluten containing foods [38]. Currently, a gluten-free diet is not recommended for patients with IBD. However, various sources discuss that patients eliminate gluten from their diet to alleviate gastrointestinal symptoms, although there is still no scientific evidence for this [39].

In the article by N. Morton et al. (2020) it is stated that 66% of patients showed improvement of gastrointestinal symptoms, and 38% of patients showed a decrease in the frequency and severity of their exacerbations on a gluten-free diet [38]. The same conclusion was made 10 years earlier by C.M. Triggs et al. (2010), although their work focused on food intolerance. They noted that specific dietary changes in the majority of subjects (>66%) reduced the number of exacerbations and the severity of gastrointestinal symptoms. In particular, it was reported that gluten-free foods often contributed to symptom reduction and were least associated with side effects [40].

C. Zallot (2013) offered 244 adults with IBD to fill out a 14-item questionnaire. After its analysis he noted that even if 9.5% of these patients believed that gluten exclusion helps to improve symptoms during exacerbations of the disease, only 1.6% actually decided to do so during its relapse [41].

A similar conclusion was made by a group of authors after a questionnaire survey of 1254 IBD patients. They indicated that patients who followed a gluten-free diet (4.7%) experienced no differences in disease activity, complications, and frequency of hospitalizations compared to patients who did not follow a certain dietary regimen. In addition, the authors noted a worsening of psychological well-being in those who followed the diet [42].

These controversial results emphasize the importance of further research, as there is still insufficient evidence to recommend the elimination of gluten from the diet of these patients, mainly because this protein is likely to be only one of many factors involved in the clinical symptoms of IBD.

At the same time, gluten-free industrial products are saturated with salt, fat, and sugar. This makes them more palatable to customers. This composition has nutritional properties of low quality and is associated with an increase in cardiovascular disease. In addition, it can predispose to inflammatory and functional gastrointestinal diseases. Finally, the absence of gluten in the diet may have a negative impact on the psychological well-being of these patients secondary to the restrictive characteristics of the diet itself. Although these data are intriguing, further research is needed before any recommendation for gluten avoidance can be made.

CELIAC DISEASE IS A RISK FACTOR FOR INFLAMMATORY BOWEL DISEASE

Celiac disease, a chronic immune-mediated enteropathy that develops as a consequence of gluten consumption, shares with IBD a multifactorial etiology resulting from a complex interaction between genetic variability, environmental factors, and dysregulation of the immune response [43].

A. Shah et al. (2019) pointed out celiac disease as a potential risk factor for IBD and demonstrated that IBD occurs more frequently in patients with celiac disease compared to the general population [44]. Children with co-morbidities (IBD and celiac disease) have been found to have specific phenotypic features with a higher risk of autoimmune diseases, colectomy and delayed puberty compared to children with IBD only [45].

A study conducted by S. Yehuda et al. (2019) showed that patients with IBD were more likely to suffer from various autoimmune diseases compared to patients without IBD [46]. In a retrospective analysis by M. Alkhayyat (2021) emphasized the significant association between celiac disease and IBD. It was noted that in ulcerative colitis the risk of celiac disease formation is higher compared to the occurrence of other autoimmune diseases [33].

E. Aghamomadi et al. (2022) found a similar pattern of expression of proinflammatory cytokines in intestinal biopsy samples from both individuals with celiac disease and IBD. Thus, these findings bring new perspectives in the search for

common potential biomarkers for diagnosis and common therapeutic targets for the treatment of these diseases [47]. Although an earlier study in adults with IBD (n=1711) was able to confirm histologically and serologically the diagnosis of celiac disease in only 0.5% of them [48].

MICROBIOME

The microbiota has been proven to play an important role in the stimulation and regulation of the immune system [49]. Dysbacteriosis observed in patients with IBD may be either the cause of localized intestinal damage or potentially one of the factors leading to chronic inflammation.

The study of the gut microbiota has revealed significant differences in healthy and IBD subjects. In IBD, a less rich composition of commensals is observed against the background of increased mucose-associated microbiota. The structure of the intestinal microcosm is characterized by a decrease in the number of representatives of the phyla *Bacteroidetes* and *Firmicutes*, which have anti-inflammatory activity. It also shows an increase in the titer of microorganisms of the phyla *Enterobacteriaceae* (in particular, *E. coli,* and its invasive strains). Specific microbiota markers of IBD have even been identified, namely, the predominance of *Enterobacteria, Proteobacteria,* adhesive *E. coli* and the deficiency of *Cl. coccoides, Faecalibacterium* [50–52].

It has been noted that during IBD exacerbation the concentration of *Bifidobacterium* spp. and *Lactobacillus* spp. is suppressed compared to remission periods. In addition, differences in the composition of microbiota have been found in IBD patients. Firstly, it was found between inflammatory and non-inflammatory regions of the intestine [53]. Secondly, it depended on the localization of the pathological process, for example, in Crohn's disease with lesions of the colon and ileum. Moreover, it has been found that in patients with ulcerative colitis, one serotype of *Escherichia coli* dominates over the other fecal microbiota [54].

The combination of imbalance between the commensal and aggressive microbiota, as well as impaired epithelial permeability, leads to perversion of the recognition of pathogen-associated molecular structures by toll-like receptors (TLRs). This is accompanied by pronounced endotoxemia, disinhibition of the early phase of inflammation and formation of specific antibodies.

It has been suggested that the causes of dysbiosis in IBD patients may be colonization of the intestine by pathogenic microorganisms, failure of immunological tolerance to their own microorganisms, or a combination of both [54].

Patients with ulcerative colitis more often have induction of Th2-lymphocytes and NKT (natural killer T cells) with high concentration of IL-4 and IL-13 with insufficient suppressor function of regulatory T cells (T-reg) and their cytokines (TGF-β and IL-10), while patients with Crohn's disease express Th1- and Th17-lymphocytes and increase the level of IL-12, IL-17, IL-23 and gamma interferon (INF-γ). It has been observed that an increase in pro-inflammatory cytokines correlates with a decrease in short-chain fatty acids [14].

Considering gluten as one of the triggering factors in the genesis of IBD, it is necessary to emphasize the microbiota. The microbiota of patients on a gluten-free diet has been found to be more similar to the healthy gut microbiome compared to the microbiota of gluten-consuming patients [55].

Lactobacillus spp. are recognized as the leading microbial species in the structure of a healthy microbiota, as they break down gluten peptides, thereby reducing their immunogenicity. The protective role of *Lactobacillus* spp. was confirmed by the work of Herrán et al. In this study, it was emphasized that this bacterium is directly involved in the process of gluten digestion, thus inactivating its immunomodulatory and cytotoxic effects on intestinal cells [56].

It has been proposed to modulate the microbiota of IBD patients with probiotics to avoid disease progression and/or reduce the intensity of the active phase.

Several studies evaluating probiotics in IBD patients have shown encouraging results. For example, the probiotic composition VSL#3, which contains *Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus debrueckii sub. Bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis* and *Streptococcus salivarius sub. Thermophilus* improved clinical symptoms in patients suffering from ulcerative colitis [57, 58].

Recent studies on inflammatory biomarkers have shown that consumption of fermented dairy products transforms the fecal microbiota and reduces markers of systemic inflammation [59–62].

The administration of fermented dairy products which contains *Bifidobacteria infantis, Bifidobacterium* breve, *Bifidobacterium bifidum* and *Lactobacillus acidophilus* provided clinical and endoscopic improvement in patients with ulcera-

tive colitis, as they had decreased plasma IL-6 concentrations compared to placebo. The effect of probiotic fermented milk products approached that of probiotics [63].

Additional prospective multicenter studies are needed to draw a final conclusion about the effectiveness of fermented dairy products in IBD.

THE ROLE OF VITAMIN D IN THE GENESIS OF INFLAMMATORY BOWEL DISEASE

Epidemiologic studies indicate that vitamin D deficiency (VDD) is widespread among patients with IBD. For example, the diseases have been found to be more common in countries of northern latitudes than in southern latitudes, which is consistent with vitamin D deficiency among the inhabitants of these regions [64].

It is well known that the production of this vitamin in the subcutaneous fat layer depends on exposure to UVB radiation through sunlight, and in climate and geographical zones located above the 60th meridian, the number of clear days is limited, and the wavelength range of UVB radiation does not provide the synthesis of vitamin D.

Due to its immunomodulatory properties, vitamin D contributes to the adequate functioning of the innate and adaptive immune response, including anti-inflammatory effects, modulating the activation, proliferation and differentiation of T- and B-cells, maintaining the integrity of the intestinal barrier and the composition of the gut microbiota. In turn, vitamin D deficiency is associated with increased susceptibility to immune-mediated diseases, including IBD [65, 66]. Low vitamin D range has been shown to correlate with disease acuity, frequent hospitalization, clinical and postoperative relapses, lack of response to biologic drugs, and poor quality of life [67, 68].

An association between IBD and single nucleotide polymorphisms (SNPs) associated with vitamin D deficiency and vitamin D receptor (VDR) has been identified [69–71].

However, in clinical studies that have demonstrated an association of low vitamin D concentrations with clinical relapse of IBD, current data have failed to establish a conclusive genetic association between the single nucleotide polymorphism of vitamin D deficiency and the vitamin D receptor with IBD [72].

A meta-analysis of several studies evaluated the interference of the VDR gene polymorphism, which is mapped to a region of chromosome 12, on the risk of ulcerative colitis and Crohn's disease. The vitamin D receptor serves as a cellular receptor for calcitriol, which exerts a wide range of different regulatory effects on the immune system [73].

Four allelic polymorphisms of the *VDR* gene *(rs731236, TaqI; rs1544410, BsmI; rs2228570, FokI; rs17879735, ApaI)* were investigated. The study finds that European carriers of *rs731236 TaqI tt* have an increased likelihood of Crohn's disease, while the presence of the *ApaI* allele reduces this risk in both Europeans and Asians. The presence of the *FokI* allele determines susceptibility to ulcerative colitis only in Asians [73].

A New Zealand study analyzed the role of serum vitamin D levels in individuals with a certain genotype on the status of Crohn's disease. Researchers found that the concentration of vitamin D in serum is significantly lower in this disease compared to healthy individuals. The presence of the allele *rs731236-A (VDR)* or *rs732594-A (SCUBE3*) in Crohn's disease had a clear correlation with vitamin D supply [74].

Low levels of vitamin D receptor are coordinated not only with chronic inflammation but also with reduced expression of the *ATG16L1* gene, which is required for autophagy and maintenance of intesti-nal homeostasis. In addition, the *ATG16L1* gene also accounts for the innate and adaptive response through the expression of dendritic cells (DCs), T- and B-lymphocytes. Recently, the vitamin D receptor has been shown to regulate *ATG16L1* gene transcription [75]. Moreover, the vitamin D-VDR complex plays a crucial role in maintaining the integrity of the intestinal barrier by inducing transcription of the gene encoding the enzyme proteintyrosine phosphatase N2 (PTPN2), which suppresses the expression of claudin-2 (a protein that increases intestinal permeability). This mechanism helps to prevent intes-tinal inflammation [76, 77].

Antimicrobial peptides such as cathelicidin and defensins also provide protection to the intestinal barrier. Vitamin D increases cathelicidin synthesis in macrophages by interacting with receptors located in the promoter region of the gene responsible for the synthesis of this protein. Vitamin D deficiency is associated with inhibition of cathelicidin expression and, consequently, with increased development of the inflammatory process [78].

CARD15/NOD2, the major IBD-related gene, is structurally similar to innate immunity proteins. The *CARD15/NOD2* gene is predominantly localized in monocytes, macrophages and dendritic cells, but can be expressed in enterocytes after activation by inflammatory cytokines (TNFa or IFN-γ) [78].

Vitamin D stimulates the expression of the *CARD15/NOD2* gene and the protein of the same name in epithelial and monocytic cells. This triggers the NF-κB pathway and enhances the antimicrobial defense of β2-defensin and cathelicidin in the presence of muramyl peptide. However, this effect is only observed in individuals with functional NOD2 protein, as Crohn's disease patients homozygous for non-functional NOD2 variants do not show this response. A significant number of mutations associated with Crohn's disease are characterized by reduced NF-κB activation when exposed to muramyl dipeptide. This observation implies that impaired anti-inflammation involving *CARD15/NOD2* may play a role in the pathogenesis of Crohn's disease or some other inflammatory disease, as the vitamin D deficiency [78].

Vitamin D is able to inhibit the IL-23 receptor pathway in innate lymphoid cells (ILC- 3), which are tissue-resident lymphocytes that functionally resemble T helper cells 17/22 in the adaptive system [79].

Circulating B cells can regulate the immune response by producing vitamin D through an autocrine mechanism, thus preventing the cascade of inflammatory reactions [80].

CONCLUSION

IBD is steadily increasing worldwide. An important role in the emergence of IBD belongs to epigenetic processes, which, in the presence of genetic predisposition, realize the effect of provoking (trigger) factors, namely, through the restructuring of the immune response form the inflammatory phenotype.

It is now proven that the widespread westernization of eating behavior leads to a significant transformation of the gut microbiome, affecting the activity of immunomodulatory genes such as *TGFβ, TGFβR, CTLA4, FOXP3*, contributing to the formation of a pro-inflammatory phenotype and a wider spread of chronic inflammatory and autoimmune diseases. Vitamin D deficiency can alter DNA methylation processes associated with genes regulating metabolic and immune functions. These disorders affect transcriptional activity and gene expression levels, determining the risk of IBD development and its course.

Thus, prevention of IBD in the presence of genetic predisposition should be aimed at a healthy lifestyle, adequate nutrition, preservation of the microbiome with constant monitoring of the immune status.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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