Review Article

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Biomarkers Journal
ISSN 2472-1646

2018
Vol.4 No.1:8

DOI: 10.21767/2472-1646.100046

Etiopathogenesis of Inflammatory Bowel Diseases

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Abstract

Non-specific Inflammatory Bowel Diseases (IBD) are particularly troublesome diseases affecting the human digestive tract, in particular the intestine. These diseases manifest themselves in chronic intestinal inflammation that is difficult to control, with periods of uncontrolled exacerbations and self-reminiscent occurrences. Depending on the symptoms and their location in the human gastrointestinal tract, these diseases may occur in various forms. Among the two most common forms of these diseases, Ulcerative Colitis (UC), and Crohn's Disease (CD) can be distinguished. Although the underlying cause of activation as well as the subsequent development of these diseases is not clearly defined, these disorders are known to have autoimmune background. The pathogenesis of IBD is associated with chronic idiopathic, recurrent, inflammatory-mediated gastrointestinal inflammation. The disease may be caused by changes in genes caused by various factors or family genetic predisposition. Exposure to a range of environmental risk factors may lead to disease activation in susceptible individuals. Many of the various factors mentioned in the article, which people are exposed to in their lives, may influence the development of these diseases.

Keywords: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease

Received: March 29, 2018; **Accepted:** April 13, 2018; **Published:** April 18, 2018

Citation: Mrowicki J, Mrowicka M, Dziki A, Dziki L, Majsterek I (2018) Etiopathogenesis of Inflammatory Bowel Diseases. Biomark J. Vol.4 No.1:8

Abbreviations: IBD: Inflammatory Bowel Diseases; UC: Ulcerative Colitis; CD: Crohn's Disease; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; OCP: Oral Contraceptive Pill; **PUFA: Poly Unsaturated Fatty Acids;** PM: Particulate Matter; GERD: Gastroesophageal Reflux Disease; MCs: Mast Cells; ROS: Reactive Oxygen Species; TNF: α-Tumor Necrosis Factor-α; CRP: C Reactive Protein; CMC: Carboxy Methyl Cellulose; P80: Polysorbate 80; SRB: Sulphate-Reducing Bacteria; VDR: Vitamin D Receptor; IECS: Intestinal Epithelial Cells; MIR346: MicroRNA 346; ESR: Erythrocyte Sedimentation Rate; hs-CRP: Highly sensitive, so-called; AIEC: Adherent Invasive *Escherichia coli*; HP: Helicobacter Pylori Infection; HHV-6B: Human Herpes Virus type 6; EBV: Epstein-Barr Virus; FAM: Fecal-Associated Microbiota; MAM: Mucosa-Associated Microbiota; CDI: Clostridium Difficile Infection.

Introduction

Both of the most common forms of these diseases in their course are substantially different from each other. UC is a chronic inflammatory process of the colon mucosa. This disease most often affects the colon, but can be extended to the sigmoid or even the entire intestine. The earliest symptoms that predict this form of the disease are abdominal pain combined with long-lasting diarrhea along with an admixture of blood and a feeling of pressure on the stool. These symptoms can quickly lead to dehydration and loss of blood. Sometimes the presence of purulent secretion is also visible next to the blood in the feces. Crohn's disease in its course may refer to the entire gastrointestinal tract from the oral cavity to the anus, and the inflammatory changes occurring here are usually fragmentary, not continuous. This type of disease is most often located in the lower part of the gastrointestinal tract, and changes in the upper segment are diagnosed in about 3% of diagnosed cases. Among the symptoms are colic stomach pain that increases during or after a meal, often located in the area of the right hip. The diarrhea present here is watery-mucous, usually without any admixture of blood. People affected by this condition report postprandial flatulence

combined with the transfer of intestinal contents combined with a feeling of fullness of the abdomen. In addition, patients with Crohn often have aphthous stomatitis and perianal changes. These diseases most often occur in the form of exacerbations, which may last for several months and temporally unspecified spontaneous remissions. Due to the disorder of the homeostasis of the whole organism by persistent chronic inflammation, these disorders are also often accompanied by parenteral symptoms; clots, cardiovascular, neurological, articular and pulmonary diseases which further aggravate the patient's discomfort.

Environmental risk factors play a very important role in the pathogenesis of IBD and their impact can be explained by the increasing number of cases worldwide. These include, among others, bacterial intestinal flora, an inadequate diet rich in highly processed foods, chemical compounds contained in food and the human environment [1]. Researchers conducted studies questioning the identification of possible environmental factors, during which an increased incidence of IBD was observed mainly among adolescents [2].

Young people usually show a greater tendency to consume processed food and abound in high-calorie fast-food products, which may partially explain the increasing number of cases in this age group. The latest research on the impact assessment of the discussed factors, covering 5 different environmental groups, confirms the close relationship of environmental factors with the activation and development of IBD in children, as also confirmed by the increase in incidence in highly developed countries [3].

Among the many environmental risk factors that patients with IBD were exposed to can be distinguished: smoking or passive exposure to tobacco smoke, use of non-steroidal anti-inflammatory drugs [NSAIDs], and Oral Contraceptives [OCP]. Later illness can also be influenced by early exposure to antibiotics in childhood and low levels of vitamin D. The diet, geography, sleep disturbances, stress experienced, ongoing as well as depression may contribute to the disease. These factors may contribute to the emergence and re-activation of inflammation manifested by exacerbation of clinical symptoms of the disease [4].

The genetic predisposition plays an important role in the development of these diseases along with the factors discussed above, and the preferred eating habits can largely decide on the activation and progression of these diseases in people who are burdened. The aim of this work is to summarize known environmental factors to which exposure increases the risk of activation and development of inflammatory bowel diseases especially in a specific group of people with hidden genetic predispositions for their development.

The Importance of Genetic Susceptibility

Increased incidence of IBD in people with sick relatives as well as racial-ethnic differences suggest genetic etiology of these diseases [5]. Epigenetic factors are only part of the total variance of the disease, they work in mutual reactions between the environment and the genome. Studies on their influence may introduce a new picture into the pathogenesis of IBD [6]. The increased frequency of IBD in developed and developing countries confirms the equal importance of environmental factors and genetic susceptibility to these diseases [7]. In about 1/5 of these cases, these diseases occur in a family-related complex inheritance, chromosome 16, which may indicate that the most vulnerable are members of families affected by the disease.

The Role of Environmental Risk Factors

The impact of diet

The very important role of diet in the development of these diseases may be indicated by the increasing prevalence of IBD in western countries, but also their stable growth in developing countries. This increase is associated with the increase in westernization of the diet, and hence the high consumption of protein, fat and sugar, with low intake of dietary fiber from fruit and vegetables into the diet. It has been shown that the type of food intake may contribute to changes in the intestinal microbiome, which in susceptible people may act pro-inflammatory and precede the development of the diseases in question [8].

Ubiquitous unhealthy fat in the diet including eating fast foods and products abounding in hardened fats containing harmful trans isomers, using large amounts of sugar with simultaneous low fiber intake was associated with a higher frequency of these diseases [9-12]. The high intake of saturated n-6 PUFAs with simultaneous low consumption of polyunsaturated n-3 PUFA also had an increased risk of IBD development. Saturated fatty acids played a significant role in inflammation by modulating intestinal microbiome and toll receptors in macrophages [13,14]. A relationship was also observed between the high consumption of all saturated and monounsaturated fats, and the increased risk of CD as well as UC [15].

Differing tests confirm the importance of the risk factors found. In addition to sugar, the relationship with the disease was perceived as an excessive consumption of animal fat and linoleic acid. The protective role was attributed to the high fiber consumption abounding mainly in soluble fibers derived from citrus fruits and vegetables. The presence of dietary fiber in the diet plays a fundamental role in the proper functioning of the digestive system. It protects the human body against the development of diseases of the large intestine, including cancer. Studies have shown that dietary intake is associated with lower disease progression in patients with CD, but does not affect UC [16].

During the exacerbation of the disease it is also recommended to limit fiber intake, and during remission avoiding alcohol and sulfur present in many products [17]. Fiber occurs as soluble and insoluble in water. The limitation of its intake during exacerbation of the disease mainly concerns the fraction of insoluble fiber, which while performing a mechanical function in the gastrointestinal tract may exert irritating effects on the intestinal wall, enhancing exacerbation of symptoms, stimulating its peristalsis, thereby reducing the time of intestinal transit. Soluble fractions whose source may be fruit and vegetables, heat

treated to facilitate digestion processes are fermented under the influence of bacteria forming the microflora of the large intestine, while favoring the multiplication of beneficial bacterial flora. They affect the differentiation and proliferation of intestinal epithelial cells [18].

While conducting studies, it was shown that butyrate deficiencies caused indirectly by deficiencies of soluble fiber may contribute to damage of the intestinal mucosa, and thus easier penetration of toxic compounds into the body. These substances may contribute to the formation of a chronic inflammatory process in the gut [19].

Soluble fiber fulfills many important tasks in the body. It is food for bacteria inhabiting the large intestine, and under the influence of enzymes secreted by it, it breaks down. It does not cause mechanical irritation of the intestinal walls, while it affects the passage of the intestinal passage. The prolonged period of presence of nutrients in the intestine has a positive effect on the treatment of diarrhea often found in IBD. This fraction of fiber also increases the volume of excreted faecal matter, swelling in the intestinal lumen with water absorption. In addition, this fiber has the ability to bind bile acids, reduces the absorption of fat, and also has the ability to absorb carcinogenic compounds from the intestine and toxic heavy metal ions, thus preventing their absorption into the blood or lymph.

Analyzes were carried out in the group of patients with IBD as a result of which in a significant part of the patients acute symptoms were observed after consumption of dairy products. Research has confirmed a strong relationship between the consumption of these products and the severity of disease [20]. It has been shown that milk violates the balance of intestinal bacteria. Because the enzyme lactase is produced in the small intestine, in patients with IBD due to intestinal damage and their excessive permeability, lactose intolerance may develop, manifested by the occurrence of bloating and diarrhea.

Air impurites

Among the environmental lifestyle factors besides the already mentioned smoking, psychological stress and a diet abounding in highly processed products, mention is also made of air pollution [21,22]. Air pollution has a direct effect on intestinal epithelial cells, the emergence of systemic inflammation and the activation of the immune system. The influence of these pollutants on the intestine occurs during PM lymphatic mucociliary clearance, and their source may also be food and water. This contributes to changes in the composition of the intestinal microflora [23]. Solid particles or other components present in the air can contribute to the mucosal defense of the host and trigger immune reactions [24].

It has been shown that solid particles introduced from food can trigger and accelerate the development of inflammatory diseases of the gastrointestinal tract, especially in genetically susceptible persons. Their penetration may occur as a result of combination of several factors, including increased intestinal permeability, clearance, decreased colonic motility and altered metabolic function and composition of the intestinal microflora [25].

When inhaling gaseous pollutants, there is exposure of the intestines to air pollution. During the study, it was observed that young people living in areas with high concentrations of sulfur dioxide show a greater tendency to develop UC, and residents of areas with high levels of nitrogen dioxide are more exposed to the development of CD. Heavy metals are also environmental compounds that can contribute to inflammatory bowel diseases. Sunk mercury causes various disorders in the gut. There may be abdominal pain, ulcers and bloody diarrhea [26].

The presence of heavy metals is associated with a wide range of toxic effects, including carcinogenicity, oxidative stress, DNA damage and effects on the immune system. It has been shown that exposure to heavy metals can also lead to dysbiosis of the intestinal microflora [27].

Microbiome of the Gastrointestinal Tract (GI) is essential for the health and efficiency of the host's digestive tract and is strongly dependent on the food it consumes. The lack of balance in the microbiome is most often related to the reduction in the diversity of microbial species, which causes intestinal microflora dysfunctions, and this promotes increased susceptibility to external pathogens. It has been observed that long-term exposure to the environment contaminated with heavy metals caused a statistically significant difference in the composition of GI microbiota both at the level of type and the amount of bacteria. In animals in the area contaminated with heavy metals, large numbers of Parabacteroides, Rikenella and pathogenic Desulfovibrio, Bilophila were observed. The shift in the dominant species of bacteria concerned the reduction in the number and diversity of a number of protective commensal anaerobes along with the aging of the human body. The results obtained during the research show that the amount of Bacteroidetes significantly increased under the influence of heavy metals, while the share of microorganisms from the Firmicutes genome was reduced. The ratio of the number Firmicutes/Bacteroidetes is a reliable determinant of the condition of human intestinal microorganisms. Toxicity of heavy metals for organisms is largely equated with oxidative stress, and the decrease in the number of probiotics may intensify the effects of its action. Current studies on toads have shown that heavy metal pollution harms the probiotics population and results in a significant reduction in both Lactobacillus and Bifidobacterium, which is more sensitive to the toxicity of heavy metals than Lactobacillus. This result was confirmed in mice exposed to Cadmium. Heavy metal pollution also affected the species diversity of GI microflora, inhibiting the growth of some intestinal flora strains [28].

The epidemiological study showed a strong positive relationship between bone lead levels and childhood obesity, which may persist in adulthood. The changed intestinal microflora is strongly associated with the increase in body weight, which may mean that exposure to Pb is a direct factor changing the intestinal microflora. The observed perinatal exposure to lead, despite its cessation at the age of 3 weeks, permanently changed the intestinal microflora and was significantly associated with the increase in body weight in adult mice aged approximately 40 weeks. The total number of aerobic and anaerobic bacteria

varied significantly depending on the group. Bacteria from the genus Pseudomonas, Enterobacter and Desulfovibrio had greater abundance in adult mice exposed perinatal to Pb than in the control group. The diversity of the intestinal microflora in the test group was disrupted and was not as resilient as in the control. The Bacteroidetes / Firmicutes ratio is important in maintaining human health, including weight determination. Obese people probably have a smaller proportion of Bacteroides than Firmicutes, this changed number shows an increased ability to draw energy from the diet, while the ratio of Bacteroides / Firmicutes increases with a decrease in fat mass. It was also observed that 2 strains Akkermansia i Desulfovibrio related to health were significantly correlated with the exposure to lead. Akkermansia was completely abolished in the group subjected to exposure, while the number of Desulfovibrio was increased. Partial protective effects of Akkermansia against obesity and inflammation were also shown [29].

The list of ecological data indicates a positive correlation between the level of air pollution and hospitalization associated with IBD [30]. In studies conducted in patients with IBD, a decreased number of Firmicutes bacteria and an increase in Proteobacteria were observed. It has been shown that dysbiosis correction therapies, including faecal transplantation- bacterial flora transplantation and the use of probiotics, give promising results in the treatment of IBD [31].

Impact of stress

It has been shown that stress affects intestinal homeostasis disorders by altering the effects of the brain and intestinal axis and may have short or long-term effects on the functions of the digestive system. Persistent exposure to stress contributes to the activation of a wide range of gastrointestinal disorders: irritable bowel syndrome, peptic ulcer, Gastro Esophageal Reflux Disease (GERD) as well as may be a factor affecting the activation of IBD. Stress can also affect the motility of the digestive system, increase intestinal sensitivity and permeability, have a negative effect on intestinal microflora and reduce the regenerative capacity of the gastric mucosa. It also has an effect on mast cells (MCs), which as a result may act as a stimulant on the cerebral-enteric axis and thus contribute to the secretion of neurotransmitters, including pro inflammatory cytokines.

Based on the conducted research, it has been proved that probiotics exert significant influence on cerebral-enteric axis interactions and inhibit stress-induced disorders in the entire gastrointestinal tract. Melatonin was also an important protective factor against the effects of stress [32].

Studies carried out in this direction have proved the relationship between the major stressors of life such as anxiety, depression or psychiatric complications and the increased risk of IBD. Stress decreased mucus secretion and increased permeability colon mice, both characteristics of IBD. It was also shown that higher levels of stress were associated with the recurrence of UC and CD symptoms. In studies conducted on a large group of patients, stress was demonstrated as the only independent predictor of the increased risk of exacerbation. Also, the presence of anxiety or depression was associated with increased disease activity and increased risk of surgery in patients with CD [26]. Although psychological interventions did not bring therapeutic benefits, high levels of stress were positively associated with the recurrence of these diseases [30].

Oxidative stress and sleep condition

Studies have shown that oxidative stress resulting from overproduction of reactive oxygen species (ROS) plays a fundamental role in initiation and progression of IBD [33]. Sleep disorders are associated with the production of inflammatory cytokines. It was demonstrated that less than 6 and more than 9 hours of sleep per day was associated with an increased risk of UC [34]. Studies confirm the relationship between sleep and the function of the immune system, inflammation, and an increase in total mortality. Severe sleep deficiencies may cause an increase in cytokine levels, including interleukin (IL) -1β IL-6, tumor necrosis factor-α (TNF- α) protein and CRP protein, which may lead to further activation of the inflammatory cascade [35].

The effect of additional substances contained in food

The etiology of IBD is not fully understood, however, it is known that these diseases develop mainly in people with a genetic predisposition under the influence of various factors: environmental, viral and bacterial. It is related to the mutual relationship between these factors and immune response of the organism. The pathogenesis of these diseases is multifactorial. The onset of the disease may occur under the influence of bacteria, food antigens, food allergens, i.e. vegetable proteins, artificial food additives: synthetic dyes, sweeteners, preservatives, chemicals contained in food: coca cola drinks, chewing gum. Among other factors, we can distinguish the gluten contained in cereals and UHT milk. The studies showed that the exclusion of gluten, yeast and dairy products from the diet translated into a two-fold prolongation of remission periods in CD in relation to results obtained under the influence of corticosteroids [36].

Harmful effect of used emulsifiers

In the latest research conducted on animal models it was shown that emulsifiers such as carrageenan and carboxy methylcellulose have been shown to cause intestinal ulcerations with histopathological features similar to those recognized in IBD. By breaking the epithelial barrier and disrupting the innate mucosal responses to microorganisms and stimulating pro inflammatory cytokines, these emulsifiers may influence the development of inflammatory bowel diseases [37]. In similar studies conducted independently, it was confirmed that the use of synthetic dietary emulsifiers contained in foods such as CarboxyMethylCellulose (CMC) and polysorbate 80 (P80) can cause inflammatory disorders and change the composition of the intestinal microflora. These emulsifiers are also used as additives for the production of certain medicines. It was also shown that dysbiosis resulting from their action may be a determining factor of colon cancer [38].

Evidence of the relationship between the use of emulsifiers in processed foods and the increased risk of IBD in the animal model is also confirmed by other researchers [39]. It is assumed that mucosal barrier defects in patients with IBD may also occur due to the use of household detergents in addition to emulsifiers in food [40].

During other independently conducted studies it was observed that emulsifiers such as carboxymethyl cellulose and polysorbate 80, contribute to the damage of the protective intestinal mucosa, contributing to intestinal inflammation by direct contact of the bacteria with the intestinal epithelium, simultaneously changing the composition of the intestinal microflora towards the formation of bacteria with properties pro-inflammatory contributing to the breakdown of the protective layer of intestinal mucus, irritating the intestine and affecting the improper functioning of the immune system, which combined with the genetic susceptibility to the development of these diseases may accelerate their activation.

The role of sulfur dioxide, iron and artificial food additives

Sulfur dioxide is another factor that is important for the activation of these diseases. It is a medium widely used for the preservation of, inter alia, dried fruit, musts and fruit pulp and some vegetable and fruit juices, as well as ice cream. Sulfites are therefore present in all fruit wines. It has been shown that sulfur dioxide is harmful not only to the respiratory system but also to the stomach and intestines of mammals [41].

Consumption of foods with a high sulfur content contributes to the rapid expansion of sulfite reducing bacteria (sulphate-reducing bacteria- SRB). SRB bacteria were found in 98% of faeces samples from UC patients. The development of SRB occurs after the consumption of highly processed food with the use of emulsifiers, artificial colors and preservatives such as; pyrosulfite, sulfur dioxide. This is also due to the mucin-sulfuric multi-sugar found in the intestinal mucus. During the growth of these bacteria, sulfur is used to form bridges in the mucin intestinal mucus. The mercaptoides formed during the reduction of sulphites together with sulphides influence the oxidation of fatty acids in colonocytes, and the n-butyrate produced at that time has the protective function of epithelial cells against the effects of harmful factors. Sulphite-reducing bacteria are involved in the etiology of UC contributing to the production of abnormal intestinal mucus through the production of highly toxic hydrogen sulphide that damages the intestinal epithelium [1]. Another pro-oxidant mediator that affects the intestinal inflammation and the mechanisms of cellular stress is iron [42].

Effect of artificial sweeteners

Factor showing inhibitory effect on the growth of commensal intestinal bacteria is saccharin. It can be a key factor predisposing to the development of IBD, because it contributes to the formation of disorders in the inactivation of digestive proteases and affects the digestion of the mucous layer and breaks the intestinal barrier. Sucralose is also suspected of similar mechanism of action [43]. The potential influence of artificial sweeteners on the development of both forms of IBD has also been confirmed on the basis of patient surveys [44].

The impact of pharmaceuticals used: NSAIDs, OCPs and antibiotics

In this study, an increased risk of IBD has been confirmed due to the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) as well as Oral Contraceptive Pill (OCP) [45]. Other analyzes have also confirmed the relationship between the use of certain pharmaceuticals; mainly analgesic, anti-inflammatory and estrogen and antibiotics, and later diagnosis of these diseases. The increased risk of IBD was associated with the disruption of the intestinal barrier by antigens or changes in the intestinal microflora. The cause of this condition was associated with the earlier use of the aforementioned pharmaceuticals, antibiotics and many drugs from other groups. Positive correlation between NSAID and IBD was confirmed by case-control studies [46].

Studies have been conducted in two cohorts of American women, as a result of which it was shown that the use of hormonal contraceptives in them was associated with the risk of CD. The link between oral contraception and the development of UC was only for women with a history of smoking [47]. The relationship between the use of OCP and the increased risk of developing IBD, mainly CD confirmed other analyzes [48,49].

Badania te Subsequent independently conducted studies confirm the thesis of the relationship between the use of OCP and its impact on the activation and development of both forms of these diseases [48]. It was shown that exposure to antibiotics in childhood interfered with the development of the correct tolerance to intestinal bacteria, which could have contributed to the subsequent development of IBD [50].

The role of pancreatic proteases

Excessive action of pancreatic proteases has been found by examining faeces from patients with IBD. The use of antibiotics may contribute to a significant reduction in the amount of intestinal bacteria and bacterial proteases, and the conducted analysis showed an increase in the number of pancreatic proteases after the treatment. Because the pancreatic proteases - trypsin and chymotrypsin are not inactivated in the lower part of the ileum due to the smaller amount of intestinal bacteria, this can be of great importance in the pathogenesis of IBD [51].

The impact of smoking

The greatest risk factor for the activation and development of IBD, which has been identified so far, is family history, resulting from genetic conditions. It may also be related to environmental factors on which family members are exposed together [52]. Smoking as well as passive daily exposure to tobacco smoke may be one of such factors. Conducted cohort studies have shown an increased risk of CD in smokers and in people who have stopped smoking. The risk of developing UC increased in them within 2-5 years from the end of the addiction [53]. Smoking is a protective factor for UC, but a risk factor for CD [54]. Smoking cessation is

an essential therapeutic strategy for patients with CD [55]. It has been shown that exposure to cigarette smoke in childhood often involved the need to carry out surgery during the CD, the risk-reducing factor was breastfeeding in childhood [56].

The role of hygiene conditions

The analyzes carried out in this direction confirmed the relationship between good sanitary conditions combined with less exposure to intestinal bacteria in the early stages of life, and inappropriate reactions of the immune system at a later time [57]. Similarly, greater exposure to intestinal organisms in a larger group of siblings reduced the risk of developing IBD at a later age [58].

Experiments conducted among British twins have shown differently that early exposure to "infections" in childhood may be associated with the subsequent development of IBD [59]. Recent research confirms the thesis that low exposure to pathogens in childhood caused by restrictive hygiene compliance may, according to the so-called "hygienic hypothesis", increase the risk of developing intestinal inflammation later in life. Because the mucous membrane of the immune system has not been prepared for combating potential risks, it may be more susceptible to the development of uncontrolled inflammation [45].

The importance of nutritional deficiencies

The researchers suggest that deficiencies of some micronutrients affect the course of the disease, by increasing the occurrence of complications and associated with this poorer quality of life of patients [60]. Patients with CD, but also with celiac disease, as well as with gastric or duodenal ulcer are particularly at risk for hypocalcaemia. It appears when calcium is badly absorbed from the gastrointestinal tract. Diseases of the duodenum and the distal part of the small intestine can significantly reduce its absorption because the absorption of calcium takes place in these organs. Among the causes of hypocalcaemia are also mentioned deficiencies of vitamin D and magnesium diagnosed with high frequency in patients with IBD. It is recommended that existing deficiencies be supplemented as soon as possible. The results of analyzes conducted among children from IBD, showed abnormalities in levels of trace elements, which may be due to insufficient intake, impaired absorption or increased losses due to the loss of intestinal absorption associated with the inflammatory process. This process may proceed as a result of the reduction of scavenging of free radicals through the deficiency of zinc and selenium, therefore it is recommended to supplement these trace elements [61].

The protective role of vitamin D

The deficiencies of vitamin D may play a significant role in the activation and development of discussed diseases. Vitamin D plays an important role in the process of calcium absorption into the bone and is also an important factor for the proper functioning of the immune system. Due to the small number of sunny days in the year as well as the addition of sunscreens in summer, vitamin D deficiencies in humans are very common. The study found a relationship between vitamin D deficiency and the occurrence of inflammatory bowel diseases. In the group of patients with IBD, there are frequent deficiencies of this vitamin as well as decreased expression of the vitamin D receptor (VDR). Increased apoptosis of Intestinal Epithelial Cells (IECS) may be partly responsible for causing inflammation and contributing to the development of the disease. Research has shown that vitamin D blocks the development of colitis by inhibiting IECS apoptosis [62].

Analyzes were carried out in people from IBD from the south-eastern and western regions of Norway. It was found that a deficiency of vitamin D among patients in these areas was very common. It was mainly associated with more frequent attacks and higher inflammatory activity of CD [63]. In tissues collected during biopsies from the human intestines, it was observed that the reduction of the epidermal VDR receptor was associated with an increase in the penetration of immune cells and increased levels of TNF-α and miR-346. In the experimentally induced murine colitis model, VDR expression decreased with the progression of the colon inflammatory process and was inversely correlated with the induction of TNF-α and miR-346 in the intestinal mucosa. As a result of these analyzes, it was noted that during TNF-α mucosal inflammation, it induces miR-346, which leads to retardation of epidermal VDR. Reduction in the amount of mucosal VDR receptor affects the deterioration of the integrity of the epithelial barrier of the mucous membrane and the severity of the inflammatory process of the large intestine [64].

Other studies also support the hypothesis that vitamin D supplementation may have a beneficial effect on UC patients. This is indicated by the reduction in Erythrocyte Sedimentation Rate (ESR) and marker for inflammatory and reumatological disease (hs-CRP) levels observed during studies, as well as the increased expression of the cathelicidin LL37 gene [65].

The role of parasites and pathogenic bacteria

Pathogenic bacteria are involved in pathogenic processes associated with the development of IBD. The infection with a group of adherent invasive E. coli bacteria (Adherent invasive Escherichia coli AIEC) was responsible for the regulation of microRNA and the reduction of protein expression needed for autophagy and the autophagy of the reaction in intestinal epithelial cells [66]. Many pathogenic bacteria are involved in the pathogenesis of IBD [67]. Among them, such as Salmonella, Campylobacter. The presence of parasites in the gastrointestinal tract was associated with a lower frequency of diagnosis of these diseases. An important protective role against the development of chronic inflammatory diseases was Helicobacter pylori infection (HP), this bacterium significantly reduced the risk of developing these diseases by increasing the protein expression associated with the functioning of regulatory T cells [67,68].

The role of viruses, the impact of pharmaceuticals

Various viruses can play a role in the pathogenesis of IBD. It has been demonstrated that the measles virus can persist in intestinal tissue and early childhood exposure to this virus can be a risk

factor for the subsequent development of CD [69]. A significant correlation was found between measles and mumps infection in the same year of life and the subsequent development of IBD, in addition, the mumps virus acquired before the age of 2 significantly increased the risk of UC. In the conducted studies, it was also observed that atypical paramyxovirus infection in childhood could be a factor increasing the risk of developing these diseases [70]. Frequent coexistence of the human herpesvirus type 6 HHV-6B and cytomegalovirus was associated with greater activity of these diseases and the need to use immunosuppressive drugs in therapy. It was found that the intensity of HHV-6B correlated with the severity of UC [71].

Epstein-Barr virus (EBV) infection has been shown in patients with IBD treated with immunosuppression to be associated with an increase in inflammation of the intestinal mucosa and an increase in the severity of the disease course. The results of the study indicate that an effective treatment strategy in these patients may be the use of anti-viral antibodies [72]. Other studies have shown that treatment with azotiopurine due to decreased immunity could increase the risk of early infection with Epstein-Barr virus (EBV) in children. The higher titer of this virus was also associated with the dose of infliximab used [73]. In samples from the area of the colon from patients with IBD, a limited presence of EBV infected cells was found, which may indicate the relationship of infection with these diseases [74]. It was demonstrated that the level of EBV antibodies in patients with IBD increased with age. The level of specific EBV antibodies in the 18-25 age group was similarly low in the general population and in the IBD group, while above this age in the group of patients the level of these antibodies was close to 100% [75].

Importance of appendectomy

Removal of the appendix was also important for the development of IBD. Studies have shown an increased risk of developing CD after appendectomy [76]. The lowest frequency of this procedure was noted among patients with UC, which suggests the protective effect of earlier appendectomy on the development of this form of the disease [77].

Meaning Intestinal Microflora

Protective role intestinal microflore

To maintain intestinal homeostasis it is important to maintain the intestinal epithelial barrier intact. The change in the composition of intestinal microflora may be influenced by the inter relationship between living conditions, hygiene, eating habits and the state of activation of the intestinal immune system [78]. A damaged intestinal mucosa may affect their permeability and, consequently, affect the immune response, which in turn may promote chronic inflammation that is difficult to control. Patients with Crohn's disease had defects in the components of the intestinal mucosal barrier, ranging from the composition of the mucus layer, to the adhesion molecules that regulate the paracellular permeability. These changes may also contribute to the maintenance of chronic inflammation of the intestinal mucosa in UC [79].

The most important function of the intestinal mucosa is to create an appropriate barrier separating its contents. It should be permeable to nutrients: water, electrolytes, which from the intestinal lumen are absorbed into the bloodstream and play an important role for the body in terms of its growth and overall development. Due to the excessive secretion of pro-inflammatory mediators in patients with IBD, there is a disturbance of the immune response in relation to intestinal bacteria. An altered barrier function separating the contents of the intestine was also observed. As a result of continuous stimulation of the mucosa of the immune system, the intestinal epithelium permeability increased, which promoted the introduction of foreign antigens of microorganisms and their toxins into the blood. The conditions of malnutrition, growth inhibition and sluggish development observed mainly in children may be related to chronic inflammation in the gut. It has been proven that the intestinal barrier function is modulated by the immune system, alcohol intake, non-steroidal anti-inflammatory drugs, intestinal pathogens and their toxins, and protease [80]. A very important role in the development of these diseases is the composition of the intestinal microflora, which is modified by the above-mentioned factors. The composition of the diet may have a short and long-term significance in forming the composition of the intestinal flora. There is a large geographical variation in the prevalence of IBD [81].

Under the influence of environmental risk factors in genetically loaded people there is overproduction of proinflammatory cytokines and disturbance of intestinal mucosa homeostasis [82]. Environmental factors initiate and contribute to the subsequent reactivation of the disease. They temporarily take part in breaking the mucous barrier, stimulating the immune response. These disorders often lead to an imbalance between useful and pathogenic intestinal bacteria. It has been shown that both CD and UC are associated with heterogeneous disorders on the genetic basis. These changes can be described as causing defects in mucosal barrier function, immunoregulation [83].

The bacterial flora plays an important role in the physiological functions of the immune system and the degradation of complex food macromolecules. It is kept under constant control of the immune system, disruption of the balance between pathogenic bacteria and normal beneficial microflora is referred to as dysbiosis - deregulation in bacterial environments. The persistence of this condition may affect the occurrence of many inflammatory disorders and contribute to the development of various diseases, including IBD [84]. IBD have a multifactorial etiology. Complex relations between environmental factors: diet, sanitary conditions, antibiotics used; the genetic and individual host immune systems may contribute to inappropriate immune responses and promote chronic inflammation. Recent research indicates that intestinal dysbiosis is considered as an essential element in the initiation of inflammation and its further complications [85]. It has also been shown that increased intestinal permeability may translate into an increased risk of developing CD [86].

The intestines are the most complex element of the immune

system. Incorrect regulation of immunity in the intestinal mucosa is considered as a factor contributing to its tissue damage and inflammation. It is believed that IBD arise as a result of an abnormal immune response to components of the normal intestinal flora in people with the appropriate genetic predisposition [87].

These changes, with the participation of many other unknown factors in genetically susceptible persons, can trigger a whole cascade of abnormal reactions from the immune system. Due to the dysregulation of mucosal immunity, the pro-inflammatory cytokines are overproduced, which the patents begin to attack healthy tissues and, as a result, lead to the formation of chronic inflammation that is difficult to control, resulting in permanent damage to the gastrointestinal tract.

Other studies conducted in this direction also prove the effect of changes in the composition of intestinal bacterial flora on the development of IBD. It has been shown that probiotics and preobiotics directly affect intestinal homeostasis by acting on the balance of beneficial and harmful bacterial species. The role of psychobiotics - a new generation of psychotropic drugs affecting the central nervous system in these diseases by affecting intestinal microflora is also described [88].

Experiments were also conducted to influence the quality of air on the composition of the intestinal microflora. It has been shown that air pollution can directly affect the intestinal epithelial cells, contributing to the modulation of the intestinal microflora, the activation of the immune system and the formation of systemic inflammation [23].

Effect of pathological microflora

The commensal bacterium that is the largest contributor to the human intestinal microflora of healthy individuals is Faecalibacterium prausnitzii. Dysbioza combined with the change in its number contributes to the occurrence of diseases [89]. This bacterium is one of the main sources of butyrate in the colon, which is a beneficial source of energy for colonocytes. It also has anti-inflammatory properties, and its low level was associated with colon cancer and Crohn's disease [90]. Other studies carried out in this direction confirm the importance of butyrate bacteria in maintaining homeostasis in [91].

It has been shown that butyric acid present in the intestine stimulates the proliferation and apoptosis of cells. The analysis of the amounts of butyrate bacteria of the genus Roseburia, Coprococcus and Ruminococcus among patients from IBD showed significantly lower levels of these, with the simultaneous growth of pathogens from the genus Escherichia, Shigella and Enterococcus. Faecal microflora FAM and microbiota associated with MMA mucosa have been altered in patients with these diseases. The reduction of these beneficial bacteria and the uncontrolled growth of opportunistic pathogens may be associated with the pathogenesis of IBD [92].

Studies have shown that strains of Faecalibacterium prausnitzii are depleted in patients with CD while the amounts of Proteobacteria, especially Escherichia coli, are increased. It has been observed that the number of these bacterial groups may be a reliable indicator of dysbiosis in this disease [93]. Bacteria participating in the etiology of IBD were presented as causative agents of these diseases. Enterococus strains are suspected to have the greatest impact on the inflammatory process. They have antioxidant defense mechanisms and are firmly attached to the intestinal epithelium to form a biofilm [94].

Cow's milk is usually poorly tolerated by people with intestinal diseases. In the course of the research it has been shown that it violates intestinal microflora homeostasis, and its fats can create favorable conditions for the development of the rare pathogenic Bilophila wadsworthia, which in people with a genetic predisposition to develop IBD may initiate a chronic inflammatory process [95].

In patients with exacerbations, Clostridium Difficile Infection (CDI) is common. Patients infected with this bacterium have worse prognosis. They have more frequent relapses, have a higher rate of colectomy and an increased risk of death. Bacteria affect the growth of infection, but it has not been clearly established whether it is the cause of the disease or only the effect of inflammation in the intestinal environment [96].

The study also found a relationship between the significant development of Caudovirales bacteriophages and an increase in the risk of IBD development [97]. Various bacterial species are involved in the pathogenesis of IBD. The composition of stool microflora of CU patients differed from healthy individuals. Reduction of R hominis and F prausnitzii strains as well as Firmicutes butyrate bacteria has been demonstrated [98]. The decreased amount of F. prausnitzii was found in the elderly, it was also associated with oxidative stress and colon cancer. It seems that this bacterium can be an indicator of a healthy intestinal bacterial flora [99]. These strains also have the ability to utilize apples for their pectin growth, which shows their significant role in the colon fermentation process.

Acknowledgement

This work was supported by grant no. 2016/23/B/NZ5/02630 from the Polish National Science Centre.

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