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THE ROLE OF MICROBIOTA IN INFLAMMATORY BOWEL DISEASES: A LITERATURE REVIEW

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ABSTRACT

The gut microbiome is an ecosystem of the digestive system that synthesizes enzymes and vitamins needed for the proper functioning of the digestive process. In addition, it plays a key function in homeostasis between the digestive and immune systems. Abnormalities in the composition of the gut microbiome have been linked to the occurrence of inflammatory bowel diseases. Numerous reports in the literature suggest that microbes, or substances produced by them, can be a treatment in themselves, or an adjunctive treatment in inflammatory bowel diseases.

Methods: In our work we used scientific sources such as publications, guidelines and textbooks.

Purposes: In this paper we have compiled information on the mechanism of action of the human gut microbiota. Its influence on the immune system, as well as the mechanism of action of processes occurring in the intestinal wall. In addition, we have compiled information on the relationship between the gut microbiota and inflammatory bowel disease alongside potential treatment and effects of probiotics, prebiotics, antibiotics and fecal microbiota transplantation. Our work focuses mainly on Crohn's disease and ulcerative colitis. We have discussed their current treatments and the possibilities and effectiveness of probiotic therapy for both diseases.

Conclusion: Intestinal flora disorders are observed both in ulcerative colitis and Crohn's disease. It is believed that it may also be one of the etiopathogenetic factors of these diseases. It has been noted that the use of probiotics in combination with standard treatment promotes remission in ulcerative colitis but has no effect in patients with Crohn's disease.

Keywords: Gut microbiome, bacteria, inflammatory bowel diseases, autoimmune system, gastroenterology, Crohn's Disease, Ulcerative Colitis, antibiotics, prebiotics, probiotics, fecal microbiota transplantation.

INTRODUCTION

The gut microbiota contains the highest number of microorganisms compared to other locations where it is

present. It is essential for the proper functioning of the digestive tract. Research indicates that there is a disturbance in the balance of the microbiota in individuals with inflammatory bowel diseases (IBD). For this reason, the gut microbiota and its changes are the subject of research due to potential new treatment possibilities for inflammatory bowel diseases. Crohn's disease and ulcerative colitis are autoimmune diseases characterized by chronic and recurrent inflammation of the intestines. The cause of these diseases remains unknown, and so far, genetic factors have been primarily attributed to their pathophysiology. Due to the increasing evidence, in line with the latest research, it is believed that the gut microbiota may also play a role in the pathophysiology of these diseases. In this paper, we will discuss abnormalities in the gut microbiota in individuals with IBD, its involvement in the pathogenesis of these diseases, and possible therapeutic solutions associated with it.

METHODS

We analyzed in detail the specialized literature and scientific articles from the Pubmed database to analyze the mechanism of action of the intestinal microbiota and its impact on inflammatory bowel diseases. We then described these diseases and focused on their treatment with probiotics.

RESULTS AND DISCUSSION

MICROBIOME

The human gut microbiome includes a total of more than a thousand different species of bacteria [52,54], which populate the gastrointestinal tract from the earliest stages of life[5, 36, 52). According to current knowledge, it is estimated that the number of bacterial cells is comparable to the total number of cells found in the human body [53]. Bacterial cells colonizing the gastrointestinal tract are essential for proper intestinal function, and are involved in the digestion of dietary fiber through the production of digestive enzymes [8] and the synthesis of essential B and K vitamins [26,52]. In addition, they are important regulators of intestinal peristalsis [52, 57] and inhibit intestinal colonization by pathogenic bacteria [11, 25, 35, 47]

In healthy humans, despite individual differences, the bacterial flora is mainly composed of Firmicutes, Bacteroidetes and Proteobacteria, with the first two types accounting for more than 90% of the flora[28, 49]In patients with inflammatory bowel disease, it has been noted that there is a change within the microflora, with a significant increase in the proportion of Proteobacteria and Bacteroidetes, while a decrease in Firmicutes [37, 42, 49]. Changes within the composition of the normal bacterial flora allow colonization by pathogenic bacterial strains and cause a disruption of the immune response, resulting in the production of pro-inflammatory cytokines (including, Interleukin 17, tumor necrosis factor, interferon gamma) that promote intestinal mucositis [49]. So far, however, no pathogenic bacterium has been discovered that is directly responsible for the cause of inflammatory bowel disease, which most often manifests itself in the form of Crohn's Disease or Ulcerative Colitis[4]

A study on mice experimentally cultured in a sterile manner, so that they did not completely possess the gut microbiome flora, provides important information on the link between disorders of the composition of the intestinal microbiome and inflammatory bowel disease. In the study, inflammatory bowel disease was induced in genetically susceptible mice after transplantation of bacterial strains associated with inflammatory bowel disease [49, 50, 58]

THE ROLE OF THE GUT MICROBIOTA ON THE FORMATION OF INFLAMMATORY BOWEL DISEASES

The microbiota of healthy individuals and those suffering from inflammatory bowel disease (IBD) differs in composition, and a dysbiotic microbiome is a major risk factor for IBD [45]. Similarities have been observed in the pathology of periodontitis and intestinal inflammation, which are due in part to the excessive growth of pathogens capable of penetrating deeper layers of tissue and their ability to evade the host's immune system, leading to dysbiosis [61]. The cascade of factors leading to IBD begins with impaired function of the intestinal mucosal epithelium, leading to its apoptosis. Conditions promote bacterial penetration into the deeper layers of the mucosa and increased activation of the host immune system [40]. Dysregulation of T-cell differentiation and abnormal activation of GALT (gut-associated lymphoid tissues) against components of the intestinal microbiota play an important role in the pathogenesis of IBD. The differentiation of Th17 cells is defined by the composition of the endogenous gut microbiota, while Treg lymphocytes play a key role in the generation of inflammation in response to commensal bacteria. An imbalance between the bacterial flora and Th17 and Treg lymphocytes is being considered as one of the possible causes of IBD. This balance is important for intestinal homeostasis. GALT is responsible for the balance between tolerance and the body's immune response to intestinal bacteria. GALT dysfunction is implicated in the pathogenesis of IBD. Damaged intestinal mucosa promotes bacterial translocation leading to activation of the immune response[6, 29]. Prolonged inflammation promotes the growth of virulent bacterial strains [40] . Despite many studies, the species responsible for the pathogenesis of IBD have not been identified. Nevertheless,

diet and environmental factors influence the occurrence of the disease [12]

Gut microbiota as a cure for IBD

The gut microbiota is gaining increasing importance in the treatment of IBD. Reconstitution of the normal microbial population has become a new therapeutic hope. Several therapeutic strategies have been developed that include antibiotics, prebiotics, probiotics, postbiotics, synbiotics and fecal microbiota transplants.

ANTIBIOTICS

According to the latest ECCO guidelines, antibiotic therapy in IBD is recommended only for complications of sepsis, bacterial proliferation, postoperative prophylaxis of infections and for the perianal form of Crohn's disease [14]. Antibiotic-induced imbalance of the gut microbiota may have a significant role in the course of both ulcerative colitis and Crohn's disease. Short-term antibiotic therapy reduces the population of susceptible bacteria leading to a decrease in the diversity of the microbiota and an increase in the likelihood of colonization by naturally resistant bacterial strains [16, 43]

PREBIOTICS

Prebiotics are non-digestible carbohydrates whose fermentation by intestinal flora supports its growth [20]. The most common prebiotics are inulin, fructooligosaccharides, mannoooligosaccharides, and lactulose, which in studies in healthy subjects increased the population of *Lactobacillus* spp. and *Bifidobacterium* spp. [19]. They cause a selective increase in the microbiota and an increase in the production of short-chain fatty acids, leading to a decrease in pH, reduced adhesion of pathogenic cells to intestinal cells, changes in the structure and function of colonocytes, stimulation of epidermal growth factor production and a decrease in the activity of pro-inflammatory cytokines [3, 25, 32, 41, 46]. Studies in animal models have shown positive effects of prebiotics on IBD [9, 33]

PROBIOTICS

Defined as "live microorganisms that, when administered in adequate amounts, exert a beneficial effect on the health of the host [23]. They exert their effects by displacing pathogens, supporting intestinal barrier function stimulating epithelial and humoral immune responses [7]. It has been suggested that in patients with IBD, the use of probiotics may prevent the colonization of pathogens and have an anti-inflammatory effect [10, 24, 27, 39, 44]. Probiotics usually include bacteria of the genera *Lactobacillus* spp., *Bifidobacterium* spp. and *Enterococcus* spp. [17]

POSTBIOTICS

According to the ISAPP definition, it is a preparation of non-living microorganisms and/or their components, exerting beneficial effects on the health of the host [48]. They may have immunomodulatory and anti-inflammatory effects [2]

SYNBIOTICS

These are preparations that are a combination of prebiotics and probiotics.

FECAL MICROBIOTA TRANSPLANTATION

Fecal microbiota transplantation (FMT) is a method of transferring the microorganisms of a healthy person (donor) into the body of a sick person (recipient) (Aguilar-Toalá et al., 2018). Such therapy has proven efficacy in the treatment of *C. difficile* infection [38, 60]. In IBD, FMT may increase the rate of clinical and endoscopic remission, while data on the risk of serious side effects and improvement in quality of life are uncertain, so the method in the treatment of IBD requires further research [22]

SAFETY

Probiotics are more effective in maintaining remission than in treating the active form of the disease. While most probiotics are well tolerated in a healthy population, only microbial preparations with proven efficacy should be used in immunocompetent and chronically ill patients. In active IBD with damage to the intestinal wall, there may be an increased risk of bacteremia, so probiotic therapy should be used with caution in such individuals

ULCERATIVE COLITIS:

This disease is one of the inflammatory bowel diseases. Its lesions occur in the large intestine and in more severe cases can lead to ulceration. The primary symptom of this disease is multiple diarrheas with an admixture of blood, which can cause symptoms of anemia. The disease is diagnosed on the basis of

colonoscopy, histopathological examination of a colon section, the presence of pANCA antibodies and also high levels of fecal calprotectin [56]

TREATMENT-INDUCTION OF REMISSION

In a disease flare, the primary goal of treatment is to stabilize the patient. Replenish water deficiencies, control electrolyte parameters. The primary drugs are ICS administered intravenously. If there is no improvement, other drugs such as cyclosporine, infliximab, adalimumab may be used intravenously.[56]

MAINTENANCE TREATMENT

All patients should have this treatment introduced so as to prevent the occurrence of relapses of this disease. The primary drug is mesalazine given orally or rectally. If this is ineffective, azathioprine, mercaptopurine can be used [56]

OPERATIVE TREATMENT

If symptoms persist despite medication, surgical treatment may be considered. Radical surgery is used, which involves removing the entire colon and performing a reconstructive proctocolectomy. However, this is an elective treatment.

In urgent situations, proctocolectomy with the creation of an ileostomy is performed [56]

USE OF PROBIOTICS

In recent decades, the effect of probiotic use on the course and progression of inflammatory bowel diseases, including ulcerative colitis, has been increasingly studied.

In another study by Matthes et al. probiotics were given to patients in increasing doses, and the result of this study showed that the rate of disease flare-ups was lower in patients receiving higher doses of probiotics [34]

There was also a study by Sood et al. in which probiotics were added in patients treated with mesalazine. They were observed to have a significantly higher rate of remission than the control group treated with mesalazine alone [55].

In this study, only the efficacy of VSL#3 probiotics were observed. Bifidobacteria nor E.coli did not have such positive effects [62]

Studies emphasize that the use of probiotics in ulcerative colitis has positive results [18]

CROHN'S DISEASE

Crohn's disease is characterized by lower amounts of Firmicutes and Bifidobacteria, mainly in areas where there is acute inflammation, while the amount of other bacteria such as Campylobacter concisus and Enterococcus faecium increases. In addition, the risk of being diagnosed with new cases of Crohn's disease has been found to increase with previous exposure to antibiotics, as this leads to iatrogenic dysbiosis. The possible beneficial effect of probiotics in Crohn's disease would be due to, among other things: restoration of the normal balance of the intestinal microbiota, inhibition of certain intestinal pathogens, blocking inflammatory mediators and local stimulation of the immune system [21].

TREATMENT OF REMISSION INDUCTION

Induction of remission in Crohn's disease involves achieving clinical remission and healing of mucosal lesions. The standard treatment of first choice is corticosteroids, administered systemically orally or intravenously [31]

Study by Schultz et al.p, 11 adult patients with active Crohn's disease were treated with a combination of corticosteroids (60 mg/day) and antibiotics, and then randomly assigned to add LGG or placebo to the treatment regimen. No difference was observed in clinical remission rates during the 6-month treatment period [51]

At present, there is no evidence that probiotics used alone or in combination with conventional treatments may be involved in inducing remission in Crohn's Disease patients [13,30]

MAINTENANCE TREATMENT

Maintenance treatment in Crohn's disease consists of maintaining remission without glucocorticosteroids, reducing the number of exacerbations and preventing complications. Immunosuppressive drugs: thiopurines or methotrexate are recommended for maintenance treatment. Currently, mesalazine is not recommended

due to a lack of evidence for its efficacy [31]. Lactobacillus GG and Lactobacillus Johnsonie used alone in maintenance treatment have not yielded positive results, both in children and adults [21]

In a study involving 132 Crohn's disease patients, there were no significant statistical differences in endoscopic recurrence rates after 90 days between patients who received VSL#3 and those who received placebo. Lower levels of inflammatory cytokines and lower recurrence rates among patients who received VSL#3 earlier (for the full 365 days) indicate that this probiotic should be further investigated for the prevention of Crohn's disease recurrence [15]

CONCLUSION

Dysbiosis occurs in both ulcerative colitis and Crohn's disease. Imbalances between the microbiota and the immune system may be one of the possible causes of IBD. Dysregulation of T-cell differentiation and abnormal activation of GALT (gut-associated lymphoid tissues) against components of the intestinal microbiota are made by dysbiosis in guts. An Imbalance between guts microbiota and lymphocytes Th17 and Treg is also an point in pathogenesis. The use of probiotics has shown positive results in inducing remission when combined with standard treatment for ulcerative colitis. However, in the case of Crohn's disease, the use of probiotics does not bring benefits. So far, the species responsible for the development of IBD have not been identified.

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